UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., TEVA NEUROSCIENCE, INC. and YEDA RESEARCH AND DEVELOPMENT CO. LTD., *Plaintiffs*, v. SANDOZ INC., SANDOZ INTERNATIONAL GMBH, NOVARTIS AG, and MOMENTA PHARMACEUTICALS, INC., *Defendants*.	Civil Action No. 08-CV-7611 (BSJ) (AJP)
TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., TEVA NEUROSCIENCE, INC., and YEDA RESEARCH AND DEVELOPMENT CO. LTD., *Plaintiffs*, v. MYLAN PHARMACEUTICALS INC., MYLAN INC., and NATCO PHARMA LTD., *Defendants*.	Civil Action No. 09-CV-8824 (BSJ) (AJP) **REDACTED VERSION**

PLAINTIFFS' PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW

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Plaintiffs Teva Pharmaceuticals USA, Inc. ("Teva USA"), Teva Pharmaceutical Industries Ltd. ("Teva Ltd."), Teva Neuroscience, Inc. ("Teva Neuroscience") (collectively, "the Teva companies"), and Yeda Research and Development Co. ("Yeda") (together with the Teva companies, "Plaintiffs" or "Teva") submit these Proposed Findings of Fact and Conclusions of Law.

I. BACKGROUND OF THE CASE

A. The Parties

1. Plaintiff and counterclaim-defendant Teva USA is a Delaware corporation with its principal place of business at 1090 Horsham Road, North Wales, Pennsylvania 19454-1090. (No. 08-cv-7611, D.I. 271 ("Stipulations"), ¶ 55.)

2. Plaintiff and counterclaim-defendant Teva Ltd. is an Israeli company with its principal place of business at 5 Basel Street, P.O. Box 3190, Petah Tikva, 49131, Israel. (Stipulations, ¶ 56.)

3. Plaintiff and counterclaim-defendant Teva Neuroscience is a Delaware corporation with its principal place of business at 901 E. 104th Street, Suite 900, Kansas City, MO 64131. (Stipulations, ¶ 57.)

4. Plaintiff and counterclaim-defendant Yeda markets and commercializes new developments emerging from the laboratories of the Weizmann Institute of Science ("Weizmann Institute"), and its principal place of business is at P.O. Box 95, Rehovot, 76100, Israel. (Stipulations, ¶ 58.)

5. Defendant and counterclaim-plaintiff Mylan Pharmaceuticals Inc. is a wholly-owned subsidiary of Mylan Inc. (referred to together as "Mylan") and a corporation organized under the laws of the State of West Virginia, having an office and place of business at 781 Chestnut Ridge Road, Morgantown, West Virginia 26505. (Stipulations, ¶ 59.)

6. Defendant and counterclaim-plaintiff Mylan Inc. is a corporation organized under the laws of the Commonwealth of Pennsylvania, having an office and place of business at 1500 Corporate Drive, Canonsburg, Pennsylvania 15317. (Stipulations, ¶ 60.)

7. Defendant and counterclaim-plaintiff Natco Pharma Ltd. ("Natco") is an Indian company with its principal place of business at Natco House, Road No. 2, Banjara Hills, Hyderabad 500 033, India. (Stipulations, ¶ 61.)

8. Defendant and counterclaim-plaintiff Sandoz Inc. ("Sandoz") is a Colorado corporation with its principal place of business at 506 Carnegie Center, Suite 400, Princeton, New Jersey 08540. (Stipulations, ¶ 62.)

9. Defendant and counterclaim-plaintiff Momenta Pharmaceuticals, Inc. ("Momenta") is a Delaware corporation with its principal place of business at 675 West Kendall Street, Cambridge, Massachusetts 02142. (Stipulations, ¶ 63.)

B. The Patents-in-Suit

10. The patents-in-suit are U.S. Patent Nos. 5,981,589 ("the '589 Patent"), 6,054,430 ("the '430 Patent"), 6,342,476 ("the '476 Patent"), 6,362,161 ("the '161 Patent"), 6,620,847 ("the '847 Patent"), 6,939,539 ("the '539 Patent") and 7,199,098 ("the '098 Patent") (collectively, "the Orange Book Patents") and U.S. Patent Nos. 5,800,808 ("the '808 Patent") and 6,048,898 ("the '898 Patent") (collectively with the Orange Book Patents, the "patents-in-suit"). (Stipulations, ¶ 64.)

11. Each of the patents-in-suit is entitled "Copolymer-l improvements in compositions of copolymers." (Stipulations, ¶ 67.) The four inventors named on the patents-in-

suit are Eliezer Konfino, Michael Sela, Ruth Arnon, and Dvora Teitelbaum. (PTX 1-9.)[1] Eliezer Konfino worked for Teva and retired from the company in December 1991. Michael Sela, Ruth Arnon, and Dvora Teitelbaum worked at the Weizmann Institute. (Stipulations, ¶ 66.)

C. Copaxone® – Teva NDA

12. Teva USA is the holder of New Drug Application ("NDA") No. 20-622, for glatiramer acetate, which was approved by the FDA on December 20, 1996. (Stipulations, ¶¶ 82, 83.)

13. Teva markets and sells glatiramer acetate under the tradename Copaxone® in the United States. (Stipulations, ¶ 84.)

14. Glatiramer acetate is a form of copolymer-1. (Sept. Tr. (Grant) 220:13-221:2; Sept. Tr. (Owens) 630:11-631:8; PTX 206 at SDZ00000031; PTX 320 at MYL0000236.)

15. Copaxone® was first offered for sale in the United States on April 2, 1997. (Sept. Tr. (Congleton) 45:14-21.)

16. Copaxone® is approved for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis ("RRMS"), including patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis. (Stipulations, ¶ 85.)

17. Each of the patents-in-suit is assigned to and owned by Yeda. (Stipulations, ¶ 68.)

[1] The following conventions are used for citations to record evidence: citations to the trial transcript from the July trial have been cited as "July Tr. ([Witness Name]) [Page:Line]"; citations to the trial transcript from the September trial have been cited as "Sept. Tr. ([Witness Name]) [Page:Line]"; citations to designated deposition testimony have been cited as "[Exhibit Number] ([Witness Name] Dep.) at [Page:Line]"; citations to trial exhibits have been listed by exhibit number. Plaintiffs' trial exhibits are cited as "PTX ___". Defendants' trial exhibits are cited as "DTX ___."

18. Teva Ltd. is the exclusive licensee of each of the patents-in-suit. (Stipulations, ¶ 69.)

19. Teva caused the Orange Book Patents to be listed in the U.S. Food and Drug Administration's ("FDA") publication, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations* ("the Orange Book"). (Stipulations, ¶ 65.)

D. Sandoz/Momenta's ANDA

20. Momenta entered into a collaboration and license agreement with Sandoz AG on June 13, 2007, regarding, among other things, the development of a generic Copaxone® product. (PTX 957 (Brugger Dep.) at 105:12-106:08; PTX 175.)

21. Sandoz submitted an abbreviated new drug application ("ANDA"), No. 90-218, on December 27, 2007, seeking approval from the FDA to manufacture and sell a generic Copaxone® product[2] before the expiration of the Orange Book Patents. (Stipulations, ¶¶ 92, 93.)

22. [redacted]

23. [redacted] The Briefing Book, among other things, described at a high level certain changes that might be made to Sandoz's manufacturing process. (PTX 913.) To date, however, no amendment to Sandoz's ANDA has been filed that makes any of the changes that the Briefing Book proposed.

[2] The product proposed in Sandoz's ANDA No. 90-218 will be referred to herein as "Sandoz's proposed glatiramer acetate product."

E. Commencement of Sandoz/Momenta Lawsuit

24. Sandoz filed with the FDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), a certification alleging that the claims of the Orange Book Patents are invalid, unenforceable, and/or would not be infringed by the manufacture, use, importation, sale or offer for sale of Sandoz's ANDA proposed glatiramer acetate product ("Paragraph IV Certification"). (Stipulations, ¶ 94.)

25. Sandoz sent a letter ("the Notice Letter"), dated July 10, 2008, to Teva USA, Teva Ltd., Teva Neuroscience and Yeda, notifying them that Sandoz Inc. had filed an ANDA for glatiramer acetate and was providing information to Teva pursuant to 21 U.S.C. § 355(j)(2)(B)(i)-(ii). (Stipulations, ¶ 95.)

26. On August 28, 2008, Teva and Yeda sued Sandoz and Momenta (collectively "Sandoz" or the "Sandoz Defendants") for infringement of the Orange Book Patents in the action captioned *Teva Pharmaceuticals USA, Inc., et al. v. Sandoz Inc., et al.*, C.A. No. 08-cv-7611 (S.D.N.Y.). (Stipulations, ¶ 97.)

27. The Sandoz Defendants counterclaimed for, *inter alia*, a declaratory judgment of non-infringement, invalidity and unenforceability of the '808 and '898 Patents. (No. 08-cv-7611, D.I. 14 at ¶¶ 89-116, D.I. 16 at ¶¶ 89-116.)

F. Mylan/Natco ANDA

28. Natco and Mylan have signed an agreement dated June 7, 2008, relating to the development and marketing of a glatiramer acetate product in the United States. (Stipulations, ¶ 87; PTX 245.)

29. On June 29, 2009, Mylan submitted an ANDA, No. 91-646, seeking approval to manufacture and sell Mylan's proposed glatiramer acetate product[3] before the expiration of the Orange Book Patents. (Stipulations, ¶¶ 86, 88.)

30. [redacted]

31. On April 19, 2011, Mylan submitted a major amendment to its ANDA. (DTX 1411.) Mylan's major amendment did not make any changes to its manufacturing process.

G. Commencement of Mylan/Natco Litigation

32. Mylan filed with the FDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), a certification alleging that the claims of the Orange Book Patents are invalid, unenforceable, and/or would not be infringed by the manufacture, use, importation, sale or offer for sale of Mylan's proposed glatiramer acetate product ("Paragraph IV Certification"). (Stipulations, ¶ 89.)

33. Mylan sent a notice letter, dated September 16, 2009, to Teva USA, Teva Ltd., Teva Neuroscience and Yeda, notifying them that Mylan had filed an ANDA for glatiramer acetate and was providing information to Teva pursuant to 21 U.S.C. § 355(j)(2)(B)(ii). (Stipulations, ¶ 90.)

34. On October 16, 2009, Teva and Yeda sued Mylan, Mylan, Inc., and Natco Pharma Ltd. (collectively "Mylan" or the "Mylan Defendants") for infringement of the Orange Book Patents in the action captioned *Teva Pharmaceuticals USA, Inc.,et al. v. Mylan Pharmaceuticals, Inc., et al.*, C.A. No. 09-cv-8824 (S.D.N.Y.). (Stipulations, ¶ 91.)

[3] The product proposed in Mylan's ANDA No. 91-646 will be referred to herein as "Mylan's proposed glatiramer acetate product."

35. The Mylan Defendants counterclaimed for, *inter alia*, a declaratory judgment of non-infringement and invalidity of the '808 and '898 Patents. (No. 09-cv-8824, D.I. 8 at ¶¶ 82-117, D.I. 34 at ¶¶ 187-224.)

H. Procedural History of the Cases

36. Plaintiffs and the Sandoz Defendants submitted claim construction briefing in October to December 2009, and a claim construction hearing was held on January 20, 2010. (No. 08-cv-7611, D.I. 68-72; D.I. 76-82; D.I. 89-93, 96-97; D.I. 102, 104-105; D.I. 114-119.)

37. The Sandoz Defendants moved for summary judgment of indefiniteness on December 23, 2009. (No. 08-cv-7611, D.I. 120-122.) Plaintiffs opposed the Sandoz Defendants' motion. (No. 08-cv-7611, D.I. 128.) In connection with their opposition, Plaintiffs submitted declarations from experts Dr. Gregory Grant and Dr. Paul Dubin. (No. 08-cv-7611, D.I. 127, 128.3.) The Sandoz Defendants subsequently moved to strike the declarations of Dr. Grant and Dr. Dubin on *Daubert* grounds. (No. 08-cv-7611, D.I. 144, 148.) On September 7, 2010, the Court denied the Sandoz Defendants' motion for summary judgment and motion to strike Dr. Grant's and Dr. Dubin's declarations. (No. 08-cv-7611, D.I. 181 at 4, 9, 11, 13.)

38. Following the denial of the Sandoz Defendants' motion for summary judgment of indefiniteness, Plaintiffs and the Sandoz Defendants submitted supplemental briefing on the Sandoz Defendants' proposed construction of the term "average molecular weight." (No. 08-cv-7611, D.I. 192-193, 204-206.)

39. On October 22, 2010, the Court ordered that the *Sandoz* and *Mylan* cases be consolidated. (No. 08-cv-7611, D.I. 200.)

40. Plaintiffs and the Mylan Defendants submitted claim construction briefing in April to July 2010. (No. 09-cv-8824, D.I. 38-39, 41; D.I. 43-45; D.I. 57-65.) The Mylan

Defendants moved for summary judgment of indefiniteness on November 15, 2010. (No. 09-cv-8824, D.I. 96-98.)

41. On August 24, 2011, the Court issued a Memorandum and Order (No. 08-cv-7611, D.I. 273; No. 09-cv-8824, D.I. 194) ("Claim Construction Order") denying Mylan's motion for summary judgment of indefiniteness and construing the disputed claim terms as follows:

- "Copolymer-1" has been construed as "a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6:2:5:1, respectively, non-uniform with respect to molecular weight and sequence, which is synthesized by polymerization of suitably protected amino acid carboxyanhydrides." (Claim Construction Order at 12.)
- "Average molecular weight" has been construed as "peak molecular weight detected using an appropriately calibrated suitable gel filtration column." (Claim Construction Order at 40.)
- "Copolymer-1 having a molecular weight" has been construed as "copolymer-1 having a peak molecular weight detected using an appropriately calibrated suitable gel filtration column." (Claim Construction Order at 40, n.10.)
- "Polypeptides composed of glutamic acid, lysine, alanine and tyrosine" has been construed as "more than one polypeptide, each consisting essentially of glutamic acid, lysine, alanine and tyrosine residues." (Claim Construction Order at 14-15.)
- "Copolymers of alanine , glutamic acid, lysine and tyrosine" is construed to mean "more than one polymer molecule, each consisting essentially of

glutamic acid, lysine, alanine and tyrosine residues." (Claim Construction Order at 15.)

- "Copolymer-l fraction" has been construed as "a portion of a copolymer-1 mixture having a narrower molecular weight distribution than the starting protected copolymer-l mixture." (Claim Construction Order at 16.)
- "Toxicity" has been construed as "the degree to which a substance exhibits negative effects in mouse mortality or RBL degranulation test." (Claim Construction Order at 44.)
- "Predetermined" has been construed to mean "determined beforehand." (Claim Construction Order at 47.)
- "Predetermined by a test reaction" has been construed as "determined beforehand by a reaction carried out to determine results of varying reaction conditions." (Claim Construction Order at 50.)

(i) July Trial

42. Starting on July 11, 2011, the Court held a trial on Defendants' inequitable conduct defense. The Court heard live testimony from the following witnesses:

(1) Plaintiffs' Witnesses

Dr. Irit Pinchasi

43. Dr. Irit Pinchasi is a former Vice President for Innovative R&D at Teva. (July Tr. (Pinchasi) 13:13-17.) She was awarded a Ph.D. in biochemistry from Tel Aviv University in 1984, and did post doctoral work at the Weizmann Institute of Science (the "Weizmann Institute"). (July Tr. (Pinchasi) 8:19-9:11.)

44. Dr. Pinchasi testified regarding the research and development of Teva's Copaxone® product; the inventions described in the patents-in-suit; the technology related to those inventions; and Teva's initial patent application filed in May 1994.

Professor Ruth Arnon

45. Professor Ruth Arnon is a named inventor on the patents-in-suit. (PTX 1.) She is currently Professor Emeritus at the Weizmann Institute and President of the Israel Academy of Sciences and Humanities. (July Tr. (Arnon) 303:14-17.) She was formerly Chairman of the Department of Chemical Immunology, Dean of the Faculty of Biology, and Vice President of the Weizmann Institute. (July Trial Tr. (Arnon) 307:16-21.)

46. Professor Arnon was awarded a Ph.D. in biochemistry from the Weizmann Institute of Science in 1960 and then completed post-doctoral studies at the Rockefeller University in New York. (July Tr. (Arnon) 305:3-7, 306:24-307:1.)

47. Professor Arnon has over 400 publications in immunology and biochemistry, and has been awarded numerous prizes in that field, including the Robert Koch Prize for Medical Sciences (Germany), the Jiminez Diaz Award for Medical Research (Spain), the Wolf Prize (international), the Israel Prize, and the Rothschild Prize (Israel). (July Tr. (Arnon) 308:3-17.) Professor Arnon is a Chevalier of the Legion D'Honneur (France) and is an elected member of the American Philosophical Society. (July Tr. (Arnon) 308:3-17.)

48. Professor Arnon testified regarding the discovery and development of copolymer-1; the inventions of the patents-in-suit; the technology related to those inventions and the initial patent application filed in May 1994.

Dr. Barbara Baird

49. Dr. Barbara Baird is the Horace White Professor and Chair of the Department of Chemistry and Chemical Biology at Cornell University. (July Tr. (Baird) 569:7-11; PTX 768.)

50. Dr. Baird was awarded a Ph.D. in chemistry from Cornell University in 1979 and was a Damon Runyon Walter Winchell Cancer Fund Fellow at the National Institutes of Health ("NIH") in the immunology branch of the National Cancer Institute. (July Tr. (Baird) 571:3-10; PTX 768.)

51. Dr. Baird is an expert in the rat basophilic leukemia ("RBL") degranulation test, and has been using the RBL test for over 30 years. (July Tr. (Baird) 572:7, 573:6-14, 576:10-12, 585:22-586:1.)

52. Dr. Baird has authored approximately 140 publications. (July Tr. (Baird) 573:15-20; PTX 769.) She has received numerous awards, including the Harold Lamport Award for Biophysics and Physiology from the New York Academy of Sciences and a National Science Foundation award for women in science and engineering. (July Tr. (Baird) 574:8-20; PTX 768.) Dr. Baird was a Guggenheim Fellow, and is a member of the American Association for the Advancement of Science in both chemistry and biology and the American Academy of the Arts and Sciences. (July Tr. (Baird) 574:8-20.)

53. Dr. Baird testified regarding the RBL degranulation test and its use by the Weizmann Institute and Teva, including in the patents-in-suit.

(2) Defendants' Witnesses

Dr. Ian Kimber

54. Dr. Ian Kimber is the chairman of the Department of Toxicology at the University of Manchester. He testified regarding toxicity testing described in the patents-in-suit.

Eugene Rzucidlo

55. Mr. Eugene Rzucidlo is an attorney at the law firm Hershkovitz & Associates. Mr. Rzucidlo testified regarding the process of patent prosecution and the prosecution histories of the patents-in-suit.

(ii) September Trial

56. Starting on September 7, 2011, the Court held a trial on Plaintiffs' infringement claims and Defendants' non-infringement and invalidity defenses. The Court heard testimony from Sandoz on its non-infringement, obviousness, and lack of enablement and indefiniteness defenses. The Court heard testimony from Mylan on its non-infringement, best mode, and obviousness defenses. At trial, Mylan presented no evidence on lack of enablement or indefiniteness and Sandoz presented no evidence on best mode. During the trial, Mylan notified Plaintiffs and the Court that it was no longer asserting that the patents are invalid based on anticipation or public use. (Sept. Tr. 1349:9-1351:24.)

57. At the September trial, the Court heard live testimony from the following witnesses:

(1) Plaintiffs' Witnesses

Jon Congleton

58. Mr. Jon Congleton is the Senior Vice President and General Manager of Teva Neuroscience. (Sept. Tr. (Congleton) 39:19-22.) He has been with Teva Neuroscience for over 15 years. (Sept. Tr. (Congleton) 41:12-13.) Prior to becoming Senior Vice President, Mr. Congleton served as both product director and director of marketing for Copaxone®. (Sept. Tr. (Congleton) 42:1-13.)

59. Mr. Congleton testified regarding the nature of Teva's business, sales and marketing of Copaxone®, and the history and state of the market for multiple sclerosis treatments.

Dr. Robert Lisak

60. Dr. Robert Lisak has been the Chairman of the Department of Neurology and Professor of Immunology and Microbiology at Wayne State University for the past 25 years. He

is also Chief of Neurology at Harper University Hospital. (Sept. Tr. (Lisak) 78:6-79:7, 84:6-11; PTX 419.)

61. Dr. Lisak received his M.D. from the College of Physicians and Surgeons of Columbia University in 1965, and conducted two years of research related to multiple sclerosis at the National Institutes of Mental Health. (Sept. Tr. (Lisak) 82:6-11, 15-17; PTX 419.)

62. Dr. Lisak is an expert in multiple sclerosis and its treatment. (Sept. Tr. (Lisak) 87:24-88:6.) He has been treating multiple sclerosis patients since 1972, and personally treats about 500 MS patients currently. (Sept. Tr. (Lisak) 79:23-80:4.) Dr. Lisak has evaluated and treated about 4,500 to 5,000 multiple sclerosis patients in his career. (Sept. Tr. (Lisak) 80:5-7.)

63. Dr. Lisak has received numerous awards including a Lifetime Achievement Award from the Consortium of Multiple Sclerosis Centers and a Doctor's Award from the Myasthenia Gravis Foundation of America. (Sept. Tr. (Lisak) 86:3-12, 86:17-87:5; PTX 419.) He was elected as an honorary member of the American Neurologic Association, and a fellow by distinction of the Royal College of Physicians of London. (Sept. Tr. (Lisak) 86:3-12; PTX 419.)

64. Dr. Lisak has published over 220 papers, in addition to reviews, book chapters, and editorials. (Sept. Tr. (Lisak) 81:3-9.) He is the editor-in-chief of the *Journal of Neurological Sciences* and is on the editorial board of the journal *Clinical Neuropharmacology*. (Sept. Tr. (Lisak) 84:12-20.)

65. Dr. Lisak was the principal investigator at Wayne State University for the first large-scale clinical study of copolymer-1 for the treatment of relapsing-remitting multiple sclerosis. (Sept. Tr. (Lisak) 106:24-107:10; PTX 597.) He was also a co-author on the study publication, Johnson, *et al.*, Copolymer 1 Reduces Relapse Rate and Improves Disability in Relapsing-Remitting Multiple Sclerosis: Results of a Phase III Multi-Center, Double-Blind,

Placebo-Controlled Trial, *Neurology*, 45:1268-76 (1995). (Sept. Tr. (Lisak) 108:5-17; PTX 597.)

66. At the time the application that led to the patents-in-suit was filed in May 1994, Dr. Lisak had been treating multiple sclerosis patients for over twenty years. Dr. Lisak testified regarding the disease of multiple sclerosis and its treatment; the long felt need for a drug like Copaxone®; the failure of others to develop safe and effective treatments for multiple sclerosis; and Defendants' infringement of claim limitations relating to treatment of multiple sclerosis.

Dr. Gregory Grant

67. Dr. Gregory Grant is a Professor of Biochemistry in Medicine and Developmental Biology at the School of Medicine at Washington University School of Medicine. (Sept. Tr. (Grant) 178:9-13; PTX 760.) He is also Director of the Protein and Nucleic Acid Chemistry Laboratories of Washington University. (Sept. Tr. (Grant) 178:14-17; PTX 760.)

68. Dr. Grant is an expert in the characterization of proteins and polypeptides using size exclusion chromatography. (Sept. Tr. (Grant) 188:11-17.) He has been performing aqueous size exclusion chromatography for over 40 years. (Sept. Tr. (Grant) 188:3-5.)

69. Dr. Grant received a Ph.D. in biochemistry from the University of Wisconsin Madison in 1975. (Sept. Tr. (Grant) 179:13-21.)

70. Dr. Grant edited a book entitled *Synthetic Peptides: A User's Guide* and served as editor of a book series entitled *Techniques of Protein Chemistry*. (Sept. Tr. (Grant) 183:4-12; PTX 760.) In addition, he has authored over 120 peer-reviewed publications. (Sept. Tr. (Grant) 182:24-183:3; PTX 760.)

71. Dr. Grant has served on several editorial boards, including the editorial board for the *Journal of Biological Chemistry*. (Sept. Tr. (Grant) 184:7-11; PTX 760.) He has also served on several advisory committees for the NIH. (Sept. Tr. (Grant) 184:15-25; PTX 760.)

72. Dr. Grant is the former president of the Association of Biomolecular Resource Facilities, which is an international organization of scientists interested in developing methods for, among other things, determining the molecular weight of polypeptides. (Sept. Tr. (Grant) 183:20-184:6; PTX 760.) He has given many invited lectures in the United States and abroad and has taught graduate level courses in analytical techniques used for proteins and polypeptides, including size exclusion chromatography. (Sept. Tr. (Grant) 185:13-186:4.)

73. Dr. Grant testified regarding the background of the chemistry and molecular weight measurement technique described in the patents-in-suit and Defendants' infringement with regard to the claim limitations relating to molecular weight. Dr. Grant also provided rebuttal testimony regarding the issues of non-obviousness, definiteness, and enablement.

Dr. George Gokel

74. Dr. George Gokel is a Distinguished Professor of Science and Associate Director of the Center for Nanoscience at the University of Missouri in St. Louis. (Sept. Tr. (Gokel) 334:3-8; PTX 774.) Dr. Gokel's research laboratory has created hundreds of synthetic peptides. (Sept. Tr. (Gokel) 336:14-16.)

75. Dr. Gokel is an expert in chemistry, including synthetic and peptide chemistry. (Sept. Tr. (Gokel) 340:4-10.)

76. Dr. Gokel received his Ph.D. in chemistry from the University of Southern California in 1971. (Sept. Tr. (Gokel) 334:22-335:4; PTX 774.) He completed a two-year post-

doctorate at UCLA under Nobel laureate Donald Cram. (Sept. Tr. (Gokel) 334:22-335:4; PTX 774.)

77. Dr. Gokel has been elected a fellow of the American Association for the Advancement of Sciences, and has received the Izatt-Christensen International Award in macrocyclic chemistry, the American Chemical Society's Midwest Award, and the Chancellor's Award in Research Creativity. (Sept. Tr. (Gokel) 337:2-16; PTX 774.)

78. Dr. Gokel has founded two journals, has served on about a dozen editorial boards, and has refereed dozens of journals. (Sept. Tr. (Gokel) 337:17-22.) He has also published about 450 papers, has written or edited about 10 books, and has given over 350 invited lectures. (Sept. Tr. (Gokel) 338:4-13.)

79. Dr. Gokel is a named inventor on about 15 patents. (Sept. Tr. (Gokel) 336:23-337:1.)

80. Dr. Gokel testified regarding the chemistry described in the patents-in-suit; Defendants' infringement with regard to the claim limitations relating to copolymer-1 and the process for making copolymer-1; and provided an overall infringement opinion. Dr. Gokel also provided rebuttal testimony regarding the issues of non-obviousness and best mode.

Dr. Nicole Sampson

81. Dr. Nicole Sampson is a Professor of Chemistry at Stony Brook University. (Sept. Tr. (Sampson) 536:6-10; PTX 436.) She is an expert in peptide and polymer chemistry. (Sept. Tr. (Sampson) 542:20-25.)

82. Dr. Sampson was awarded a Ph.D. in chemistry from UC Berkeley and did a post-doctoral fellowship at Harvard University. (Sept. Tr. (Sampson) 537:1-11; PTX 436.) She

teaches graduate and undergraduate courses in organic reaction mechanisms, physical organic chemistry, and chemical biology. (Sept. Tr. (Sampson) 539:1-7.)

83. Dr. Sampson has authored over 70 peer-reviewed publications, and has been a peer reviewer for many journals, including the *Journal of Organic Chemistry*. (Sept. Tr. (Sampson) 539:17-25.) She has also given over 100 invited lectures at scientific meetings, universities, and corporations. (Sept. Tr. (Sampson) 541:16-20.)

84. Dr. Sampson is a named inventor on three U.S. patent applications, including applications related to methods of preparing polymers and polymer chemistry. (Sept. Tr. (Sampson) 542:4-9; PTX 436.)

85. Dr. Sampson has received several awards for her work in peptide chemistry, including the Pfizer Award in Enzyme Chemistry from the American Chemical Society as well as the American Chemical Society's Cope Scholar Award in Organic Chemistry. (Sept. Tr. (Sampson) 541:21-542:3; PTX 436.)

86. Dr. Sampson testified regarding Defendants' infringement with regard to the copolymer-1 claim limitations under the doctrine of equivalents and provided rebuttal testimony on the issue of non-obviousness.

(2) Mylan's Witnesses

Dr. Walter Owens

87. Dr. Walter Owens is the Vice-President of Global Research and Development at Mylan. (Sept. Tr. (Owens) 594:8-17.) He testified regarding the development of Mylan's generic Copaxone® product, including Mylan's use of universal calibration and testing of its proposed product on the experimental autoimmune encephalomyelitis model.

Dr. Stephen Kent

88. Dr. Stephen Kent is a professor of chemistry, biochemistry, and molecular biology. (Sept. Tr. (Kent) 648:9-15.) He testified regarding Mylan's best mode defense and provided rebuttal testimony regarding Mylan's infringement with regard to the copolymer-1 claim limitations.

Dr. Allen Zeiger

89. Dr. Allen Zeiger is a retired professor of biochemistry and molecular biology at Jefferson Medical College, Thomas Jefferson University. (Sept. Tr. (Zeiger) 785:2-12.) He testified regarding Mylan's obviousness defense.

Dr. Susan Rice

90. Dr. Susan Rice has her own consulting firm, Susan A. Rice and Associates, Inc. (Sept. Tr. (Rice) 995:23-996:10.) She testified on behalf of Mylan regarding toxicity data disclosed in the patents-in-suit, and whether the data demonstrate that the claimed copolymer-1 has unexpected results over the prior art.

Dr. Ari Green

91. Dr. Ari Green received his M.D. in 2001 from the University of California, San Francisco, where he is now an Assistant Professor of Neurology and the Assistant Director of the Multiple Sclerosis Center. (Sept. Tr. (Green) 1354:16-23; PTX 1964.) He provided testimony on behalf of Mylan regarding secondary considerations of non-obviousness

(3) Sandoz's Witnesses

Dr. John Bishop

92. Dr. John Bishop is Senior Vice President, Pharmaceutical Sciences, at Momenta. (Sept. Tr. (Bishop) 1062:25-1063:5.) He testified regarding the development of Momenta's generic Copaxone® product.

Dr. Trevor Laird

93. Dr. Trevor Laird owns Scientific Update, a company that develops training courses and consults for pharmaceutical companies. (Sept. Tr. (Laird) 1112:25-1113:7.) He testified regarding Sandoz's obviousness defense and provided rebuttal testimony on Sandoz's infringement with regard to the "test reaction" claim limitations.

Dr. Carl Scandella

94. Dr. Carl Scandella is the owner of his own biotechnology consulting firm. (Sept. Tr. (Scandella) 1169:15-18.) He testified on behalf of Sandoz regarding its lack of enablement and indefiniteness defenses.

Dr. Randolph Wall

95. Dr. Randolph Wall is a professor of microbiology, immunology, and molecular genetics at the UCLA School of Medicine, and Associate Director of the UCLA Broad Stem Cell Center. (Sept. Tr. (Wall) 1747:14-18.) He was a rebuttal witness for Sandoz regarding its lack of enablement and indefiniteness defenses.

(iii) Witnesses Testifying by Deposition

96. The parties have submitted designated deposition testimony from several witnesses including the following: Weizmann Institute employees Professor Ruth Arnon and Dr. Michael Sela; current or former Teva employees Dr. Irit Pinchasi, Eliezer Konfino, Dr. Alexander Gad and Dr. Haim Varkony; Mylan employees Dr. Stephen Wayne Talton and Dr.

Ross Wallingford; Natco employees Dr. Bhujanga Rao, Dr. Duddhi Linga Rao and Dr. Satyanarayana Kota; current or former Momenta employees Dr. Corinne Bauer, Dr. Steve Brugger, Dr. Ganesh Venkataraman and Dr. Mani Iyer; Sandoz employees Dr. Anup Ray and Shrinvasa Rao; and defendants' expert witnesses Dr. Jerard Hurwitz (Mylan) and Dr. Frantisek Svec (Sandoz), who were not called to testify at trial.

II. THE PATENTS-IN-SUIT

97. Each of the Patents-in-Suit is entitled "Copolymer-l improvements in compositions of copolymers." (Stipulations, ¶ 67.) The four inventors named on the patents-in-suit are Eliezer Konfino, Michael Sela, Ruth Arnon, and Dvora Teitelbaum. Eliezer Konfino worked for Teva and retired from the company in December 1991. Michael Sela, Ruth Arnon, and Dvora Teitelbaum worked at the Weizmann Institute. (Stipulations, ¶ 66.)

98. The Patents-In-Suit each claim priority to (i) U.S. Patent Application No. 08/248,037, filed May 24, 1994 ("the '037 application"), abandoned, and (ii) Patent Application No. 08/344,248, filed November 23, 1994 ("the '248 application), also abandoned. (Stipulations, ¶¶ 79-80.)

A. The Specification

99. The patents-in-suit are directed to improved compositions of copolymer-1. (PTX 1, col. 1:1-2.)[4] The patents explain that the improved compositions consist of a lower molecular weight form of copolymer-1 that may be used for the treatment of multiple sclerosis. (PTX 1, col. 1: 43-53.)

[4] The substantive portion of the patent specification is identical for each of the patents-in-suit. For ease of reference, citations are to the specification of the '808 patent.

100. The patent specification defines the molecular weight characteristics of the lower molecular weight copolymer-1 in several ways. The patent specification explains that the lower molecular weight copolymer-1 can be substantially free of species over 40 kDa, and it describes a preferred composition that has "less than 5% of species" having a molecular weight over 40 kDa. The patents also describe a more preferred composition having "less than 2.5% of species" having a molecular weight over 40 kDa. (PTX 1, col. 1:64–col. 2: 4.)

101. The patents also describe the claimed lower molecular weight copolymer-1 as "having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa." (PTX 1, col. 2, lines 5-7.) As described further, *infra*, a "molar fraction" in this context refers to the proportion of molecules (as measured by the number of "moles" of molecules[5]) between 2 kDa and 20 kDa, as compared to the total number (or "moles") of all of the molecules in the sample.

102. Finally, the lower molecular weight copolymer-1 is defined in the patent by its "average molecular weight." The patent specification provides various ranges for the "average molecular weight" values for the lower molecular weight copolymer-1, and those ranges are reflected in the asserted claims, which are discussed below. As discussed in greater detail in section IV.B., the patents also describe a synthetic process for making the claimed copolymer-1. (PTX 1, col. 4:28–col. 6:3.)

103. The patent specification describes two ways of producing a lower molecular weight copolymer-1. (PTX 1, col. 2:14-41, col. 2:51–col. 3:18, col. 4:28 – col. 6:3.) First, in Example 1, the patents describe making copolymer-1 and then "fractionating" – or dividing into

[5] A "mole" is simply a way of expressing the number of molecules. It is the number of atoms in 12 g of pure carbon-12 or approximately 6.022×10^{23} (Avogadro's number). (Sept Tr. (Gokel) 379:14-19.)

smaller portions – the resulting copolymer-1 to isolate a low molecular weight fraction. (PTX 1, col. 2:57–col. 3:2.) In addition, the patents provide examples describing processes for making copolymer-1 of varying molecular weights. (PTX 1, col. 4:28-col. 6:3.) Second, the patent describes the use of a particular reagent in the synthetic process—hydrobromic acid in the form of hydrogen bromide ("HBr") in acetic acid—to cleave an intermediate product called protected copolymer-1 polypeptides into smaller polypeptides. The patent teaches that the time and temperature of the HBr/acetic acid treatment step can be varied to control the amount of cleavage that occurs, and hence, the molecular weight of the resulting copolymer-1. (PTX 1, col. 4:59-col. 6:3.)

104. The patent specification describes the use of a calibrated size exclusion chromatography column, Superose 12, to measure the molecular weight distribution and average molecular weight of copolymer-1 samples. (PTX 1, col. 3:6-13.)

105. Example 2, entitled "Toxicity Analysis," appears in the specification of each patent-in-suit and describes two different toxicity tests, the *in vivo* mouse test and the *in vitro* RBL degranulation test. (PTX 1, col. 3:21–col. 4:27.) Example 2 describes measuring the toxicity of copolymer-1 using these two tests.

106. Referring to the *in vivo* mouse test, Example 2 states that "[t]hree batches of copolymer-1 having an average molecular weight of 7.3 and 8.4 KDa (less than 2.5% copolymer-1 species over 40 KDa) and 22 KDa (more than 5% copolymer-1 species over 40 KDa) were subjected to the toxicity test" in which five mice in each experimental group were injected with the test solution. (PTX 1 at col. 3:23-40.) Example 2 further states that "[if], at the end of 48 hours, all the animals were alive and no adverse signs had been observed, then the

batch was designated 'non-toxic'" and if "one or more of the mice had died or had shown adverse signs, then the batch was designated 'toxic'." (PTX 1 at 3:36-40.)

107. Example 2 concludes that "the batches with the average molecular weight of 7.3 and 8.4 KDa were both designated 'non-toxic', whereas in the batch with the average molecular weight of 22 KDa, 3 out of 5 mice had died at the end of 48 hours, and it was consequently designated 'toxic.'" (PTX 1 at 3:41-45.)

108. Example 2 also describes testing in the *in vitro* RBL degranulation test. Example 2 explains that the purpose of the *in vitro* RBL degranulation test was to "screen out those batches of copolymer-1 which invoke substantial degranulation and thus *might* elicit undesirable local and/or systemic side effects." (PTX 1 at col. 3:63-67 (emphasis added).)

109. Example 2 reports that "[f]our batches of copolymer-1, with average molecular weight between 6,250-14,500, were analyzed for both % of the species with molecular weight over 40 KDa and for degranulation of RBL's" in the *in vitro* RBL degranulation test. (PTX 1 at col. 4:11-15.)

110. Example 2 set forth the results of the *in vitro* RBL degranulation test in the following table:

Average M.W. (Daltons)	% of species with M.W. over 40 KDa	% Serotonin Release
6,250	<2.5	12.4
7,300	<2.5	21.0
13,000	>5	66.9
14,500	>5	67.8

(PTX 1 at col. 4:15-24.)

111. Example 2 concludes with respect to the RBL test data that "[a]s can be seen,

when the % of high molecular weight species is low (<2.5), the % release of serotonin indicative of toxicity is low, and vice versa." (PTX 1 at col. 4:25-27.)

112. The patent specification also describes pharmaceutical compositions comprising the lower molecular weight copolymer-1, as well as the treatment of multiple sclerosis using the same. (PTX 1, col. 1:51-53.)

B. The Claims

113. Prior to the trial, Plaintiffs voluntarily limited the number of asserted claims to narrow the issues for trial. The asserted claims of the patents-in-suit are claim 1 of the '808 patent; claim 1 of the '589 patent; claims 1, 2 and 3 of the '898 patent; claims 1, 2 and 3 of the '430 patent; claim 1 of the '476 patent; claim 1 of the '161 patent; claims 1 and 6 of the '847 patent; claims 1, 8, 9, 10, 12, 23, 30 and 31 of the '539 patent; and claims 1 and 8 of the '098 patent. Plaintiffs have asserted claim 3 of the '430 patent and claim 3 of the '898 patent against Mylan only.

114. The asserted claims of the patents-in-suit claim, *inter alia,* copolymer-1 with lower molecular weight characteristics, methods of making lower molecular weight copolymer-1, pharmaceutical compositions comprising lower molecular weight copolymer-1, as well as methods of treating multiple sclerosis using the claimed lower molecular weight copolymer-1. The asserted claims contain limitations relating generally to one or more of the molecular weight of the claimed copolymer-1, the process for making the claimed copolymer-1 and the use of the claimed copolymer-1 for treating multiple sclerosis. They are arranged in this manner for further discussion below. (PTX 1-9.)

(i) Molecular Weight Claim Limitations

115. All but three of the 22 asserted claims of the patents-in-suit include numerical limitations directed to molecular weight attributes of either the copolymer-1 end product and/or

an intermediate product called trifluoroacetyl copolymer-1. The molecular weight limitations can be categorized as "average molecular weight" and "molar fraction" limitations. (PTX 1-2; PTX 4-9.) In addition, three of the asserted claims are directed to a "predetermined molecular weight profile," and have no numerical limitations. (PTX 3.)

(1) Average Molecular Weight Limitations

116. Claim 1 of the '808 patent, claim 1 of the '589 patent, claims 1 and 6 of the '847 patent and claims 1, 8, 9, 10, 12, 23, 30 and 31 of the '539 patent are directed to copolymer-1 having an "average molecular weight" falling within a particular numeric range. (PTX 1; PTX 2; PTX 7; PTX 8.) For example, claim 1 of the '539 patent provides:

> A copolymer-1 composition comprising a mixture of polypeptides composed of glutamic acid, lysine, alanine and tyrosine, wherein the mixture has ***an average molecular weight of about 4 to about 9 kilodaltons***, wherein the mixture of polypeptides is non-uniform with respect to molecular weight and sequence, and wherein the composition is suitable for treating multiple sclerosis.

(PTX 8, col. 5:18-24.)

117. The asserted claims containing "average molecular weight" limitations require copolymer-1 having an average molecular weight of "about 5 to 9 kilodaltons" (claim 1 of the '808 patent, claim 1 of the '589 patent), "about 4 to about 9 kilodaltons" (claims 1 and 6 of the '847 patent, claims 1, 8, 9, 12, 23, 30 and 31 of the '539 patent), and "6.25 to 8.4 kilodaltons" (claim 10 of the '539 patent). (PTX 1; PTX 2; PTX 7; PTX 8.)

(2) Molar Fraction Limitations

118. Several of the asserted claims include limitations relating to the molecular weight distribution of a sample of copolymer-1 or the intermediate TFA copolymer-1. These "molar fraction" limitations are expressed as a certain percentage of the copolymer-1 polypeptides (or TFA copolymer-1 molecules) having molecular weights falling within a molecular weight range

or above a particular molecular weight value. (PTX 4; PTX 5; PTX 6; PTX 8; PTX 9.)

119. Claim 1 of the '430 patent exemplifies the copolymer-1 molar fraction and TFA copolymer-1 molar fraction limitations:

> Copolymer-1 having ***over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa***, prepared by a process comprising the steps of:
>
> reacting protected copolymer-1 with hydrobromic acid to form ***trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa***, wherein said reaction takes place for a time and at a temperature predetermined by test reaction, and treating said trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa with aqueous piperidine solution to form copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2kDa to about 20kDa.

(PTX 4, col. 5:21–6:8.)

120. The copolymer-1 "molar fraction" limitations include "over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa" ('430 patent, claims 1-3); "less than 2.5% … over 40 kilodaltons" ('539 patent, claims 8 and 30); "less than 5% … over 40 kilodaltons; and .. over 75% … within a molecular weight range of about 2 kilodaltons to about 20 kilodaltons" ('476 patent, claim 1; '161 patent, claim 1; '098 patent, claim 1); and "less than 2.5% … above 40 kDa" ('539 patent, claims 9, 10 and 31; '098 patent, claim 8). (PTX 4; PTX 5; PTX 6; PTX8; PTX9.)

121. All of the TFA copolymer-1 molar fraction limitations require "trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa" ('430 patent, claims 1-3; '476 patent, claim 1; '161 patent, claim 1). (PTX 4; PTX 5; PTX 6.)

(3) Predetermined Molecular Weight Profile Limitations

122. Claims 1, 2 and 3 of the '898 patent do not include any numerical molecular weight limitations; rather, they require that the copolymer-1 have a "predetermined molecular weight profile." (PTX 3.) As an example, claim 1 of the '898 patent provides:

> A method of manufacturing ***copolymer-1 of a predetermined molecular weight profile***, comprising the steps of: selecting a predetermined molecular weight profile, reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1 having the predetermined molecular weight profile, wherein said reaction takes place for a time and at a temperature predetermined by test reaction, and treating said trifiuoroacetyl copolymer-1 having the predetermined molecular weight profile with aqueous piperidine solution to form copolymer-1 having the predetermined molecular weight profile.

(PTX 3, col. 5:35-6:11.)

(ii) Process Limitations

123. Twelve of the asserted claims are directed either to a method of manufacturing copolymer-1 having the desired molecular weight characteristics or to copolymer-1 that is made by a particular process. Although the details of each claim may vary, claim 1 of the '589 patent is illustrative of the claims directed to a process for making the claimed copolymer-1:

> Copolymer-1 having a molecular weight of about 5 to 9 kilodaltons, ***made by a process*** comprising the steps of:
>
> reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1, treating said trifluoroacetyl copolymer-1 with aqueous piperidine solution to form copolymer-1, and purifying said copolymer-1, to result in copolymer-1 having a molecular weight of about 5 to 9 kilodaltons.

(PTX 2, col. 6:4-13.)

124. The asserted process for making and product-by-process claims are claim 1 of the '808 patent, claim 1 of the '589 patent, claims 1-3 of the '898 patent, claims 1-3 of the '430 patent, claim 1 of the '476 patent, claim 1 of the '161 patent, and claims 1 and 6 of the '847

patent. Claims 1-3 of the '898 patent; claims 1-3 of the '430 patent; claim 1 of the '476 patent and claim 1 of the '161 patent also require that the HBr treatment step "take[] place for a time and at a temperature predetermined by test reaction." (PTX 3; PTX 4; PTX 5; PTX 6.)

(iii) Treatment of Multiple Sclerosis

125. Ten of the asserted claims include limitations relating to the treatment of multiple sclerosis. Claim 1 of the '476 patent and claims 23, 30 and 31 of the '539 patent are directed to methods for treating multiple sclerosis. Claim 1 of the '161 is directed to "[a] composition for the treatment of multiple sclerosis." Claims 1 and 8-10 of the '539 patent recite "wherein the composition is suitable for treating multiple sclerosis." Claim 12 of the '539 patent recites "a dose therapeutically effective to treat multiple sclerosis of a copolymer-1 composition." (PTX 5; PTX 6; PTX 8.)

(iv) Pharmaceutical Composition

126. Four of the asserted claims include limitations relating to the use of the lower molecular weight copolymer-1 as a pharmaceutical composition. Claims 12, 23, 30 and 31 of the'539 patent are directed to the use of lower molecular weight copolymer-1 as a pharmaceutical composition. (PTX 8.) For example, claim 12 of the '539 provides:

> A pharmaceutical composition comprising:
>
> a dose therapeutically effective to treat multiple sclerosis of a copolymer-1 composition, wherein the copolymer-1 composition comprises a mixture of polypeptides composed of glutamic acid, lysine, alanine and tyrosine, wherein the mixture has an average molecular weight of about 4 to about 9 kilodaltons, wherein the mixture of polypeptides is non-uniform with respect to molecular weight and sequence; and
> a pharmaceutically acceptable excipient.

(PTX 8, col. 5:54-63.)

III. BACKGROUND ON THE WEIZMANN INSTITUTE'S AND TEVA'S WORK ON COPOLYMER-1

A. Multiple Sclerosis

127. Multiple sclerosis ("MS") is an inflammatory disease of the central nervous system first recognized in the 1860s by the French neurologist Jean-Martin Charcout. (*See* Sept. Tr. (Lisak) 88:8-89:18.)

128. MS is an unpredictable disease involving two of the most complex systems in the body – the immune system and the central nervous system. (Sept. Tr. (Lisak) 136:3-10.) In persons afflicted with MS, autoimmune cells attack myelin, a protective sheath wrapped around nerves found in the brain and the spinal cord. (Sept. Tr. (Lisak) 88:8-89:4.) This leads to the degeneration of myelin and, eventually, the degeneration or death of underlying nerve cells. (Sept. Tr. (Lisak) 90:4-92:11.)

129. This degeneration process eventually prevents the central nervous system from functioning properly as the brain is no longer able to send or receive messages to and from various parts of the body and other functions of the brain or spinal cord are impaired. (Sept. Tr. (Lisak) 90:4-92:11.) The immune system's attack on myelin causes multiple lesions or scars to form on the brain as well as the spinal cord as MS progresses. (Sept. Tr. (Lisak) 89:11-15.) The appearance of these multiple scars or scleroses accounts for the disease name "multiple sclerosis." (Sept. Tr. (Lisak) 89:11-15.)

130. The most common form of MS is Relapsing-Remitting Multiple Sclerosis ("RRMS"). (Sept. Tr. (Lisak) 96:17-19.) Approximately 85% of all MS patients have the Relapsing-Remitting form of the disease. (Sept. Tr. (Lisak) 89:11-15.) Patients with RRMS experience periodic relapses or attacks which are accompanied by steadily worsening disability as the functioning of the nervous system becomes more impaired over time. (Sept. Tr. (Lisak)

95:16-96:25.)

131. The symptoms of RRMS include blurred and double vision, loss of balance and coordination, tremors, fatigue, bladder and bowel dysfunction, paralysis, and even death in some patients. (Sept. Tr. (Lisak) 92:20-93:21.) Patients may exhibit different neurologic symptoms at various times and many patients become permanently disabled. (Sept. Tr. (Lisak) 92:20-93:21.)

132. The initial onset of MS typically occurs early in life - between the ages of 20 and 40. (Sept. Tr. (Lisak) 94:10-18.) As Dr. Robert P. Lisak, a practing neurologist, testified, the disease thus strikes patients in the "prime of life" - right at the time when they are beginning their careers, finishing school, or beginning to raise a family. (Sept. Tr. (Lisak) 94:10-18.) There is no way to predict when relapses associated with MS will occur and thus the disease acts like a "hanging sword," threatening sufferers with future attacks of unknown length that may result in increased or complete disability. (Sept. Tr. (Lisak) 97:1-9.)

133. Prior to the 1990s, there were no treatments available to prevent relapses or slow the progression of disability associated with MS. (Sept. Tr. (Lisak) 102:2-9; Sept. Tr. (Green) 1391:21-1392:4.) A physician's only option was to treat a patient's symptoms and to try to shorten the duration of a relapse. (Sept. Tr. (Lisak) 102:2-9; Sept. Tr. (Green) 1391:21-1392:4.)

B. Discovery of Copolymer-1 at the Weizmann Institute

134. Professor Ruth Arnon, Professor Michael Sela and Dr. Dvora Teitelbaum are Ph.D. immunologists who worked together at the Weizmann Institute, a world-renowned research institute located in Rehovot, Israel. (July Tr. (Pinchasi) 9:12-20; 16:11-17:5; July Tr. (Arnon) 302:23-303:13, 304:11-17; 304:18-305:14.)

135. In about 1966, Professor Arnon and her colleagues became interested in studying an autoimmune disease called experimental autoimmune encephalomyelitis ("EAE"), which is an animal model for multiple sclerosis. (July Tr. (Arnon) 309:11-310:10.) It was recognized by

that time that EAE was induced by a single protein called myelin basic protein ("MBP"), but nothing was known about the mechanism of the disease. (July Tr. (Arnon) 309:11-310:10.) Professor Arnon and her colleagues theorized that if they could produce a synthetic polymer that mimicked MBP, it could be used as a research tool to study the mechanism of EAE. (July Tr. (Arnon) 309:11-311:8.)

136. Professor Arnon and her colleagues synthesized three synthetic polymers, which they called copolymer-1, copolymer-2 and copolymer-3. The copolymers differed in their amino acid composition, but were all targeted to have a molecular weight of 23,000 daltons, which was the molecular weight of MBP. (July Tr. (Arnon) 310:11-311:8.)

137. Professor Arnon and her colleagues tried without success for over a year to use the synthetic copolymers to induce EAE in animals. (July Tr. (Arnon) 310:11-23.) Eventually, it occurred to them that the synthetic copolymers they had made were not similar enough to MBP to induce EAE, but might be similar enough to MBP to compete with it and prevent its activity. (July Tr. (Arnon) 310:11-23.)

138. The experiments they set up to test their hypothesis were successful. (July Tr. (Arnon) 310:11-23.) Instead of inducing EAE, copolymer-1 was very effective in suppressing EAE. (July Tr. (Arnon) 310:24-311:13.) The other two copolymers were much less effective. (July Tr. (Arnon) 311:9-13.)

139. At the time of their discovery that copolymer-1 was effective in suppressing EAE, there were practically no treatments available for multiple sclerosis. (July Tr. (Arnon) 311:14-23.) The only options for patients were immunosuppressive drugs, but these had very severe side effects and were not routinely used. (July Tr. (Arnon) 311:14-23.)

140. Professor Arnon and her colleagues published their initial findings in 1971 in the

European Journal of Immunology ("1971 Teitelbaum article"). (PTX 499.) The article described copolymer-1 as having a molecular weight of 23,000 daltons. (July Tr. (Arnon) 311:24-312:22; PTX 499 at 242.)

141. In 1974, the PTO granted U.S. Patent No. 3,849,550 (the '550 Patent") to Yeda. (DTX 1219.) The patent named Professor Arnon, Professor Sela, Dr. Teitelbaum and their co-workers as inventors, and disclosed and claimed the copolymers that they discovered could treat EAE. (DTX 1219.)

C. The Bornstein Clinical Trial

142. The first placebo controlled clinical study of copolymer-1 for the treatment of multiple sclerosis was conducted by Professor Murray Bornstein of the Albert Einstein College of Medicine in New York (the "Bornstein trial"). (July Tr. (Arnon) 316:6-15; July Tr. (Pinchasi) 22:4-24; Sept. Tr. (Lisak) 108:25-104:13.) Fifty patients were enrolled in the pilot trial, 25 of whom received copolymer-1. (Sept. Tr. (Lisak) 109:24-110:4; PTX 31 at 408.)

143. Professor Arnon and her colleagues at the Weizmann Institute participated in the basic design of the Bornstein trial and supplied Dr. Bornstein with copolymer-1 for use in the trial. (July Tr. (Arnon) 316:16-21.) The copolymer-1 they supplied was intended to have a molecular weight of 23,000 daltons in order to match the molecular weight of MBP. (July Tr. (Arnon) 316:22-317:11.) The batches, however, actually ranged from 14,000 to 23,000 daltons. (July Tr. (Arnon) 317:12-15; Sept. Tr. (Lisak) 110:11-21; PTX 31 at 408.)

144. The results of the Bornstein trial were published in 1987 in the New England Journal of Medicine ("1987 Bornstein article"). (July Tr. (Arnon) 327:22-328:9; Sept. Tr. (Lisak) 108:25-109:13; PTX 31.) While the results from that study were encouraging, they did not definitively establish whether the copolymer-1 composition studied was a safe and effective treatment for RRMS. (PTX 31 at 408; Sept. Tr. (Lisak) 108:25-111:22.)

D. Toxicity Testing Of Copolymer-1 By the Weizmann Institute

145. During the Bornstein trial, Dr. Bornstein notified Professor Arnon and her colleagues that some of the patients were experiencing local injection site reactions and that, on rare occasions, some patients experienced systemic side effects that included difficulty breathing, palpitations, severe flush, sweating and severe anxiety. (July Tr. (Arnon) 317:16-320:6; July Tr. (Pinchasi) 23:17-24:23; PTX 28.)

146. Dr. Bornstein's reports of these side effects in his patients were of grave concern to Professor Arnon. (July Tr. (Arnon) 320:7-16.) She knew that copolymer-1 was to be given to patients on a daily basis, so any side effects would be a severe issue. (July Tr. (Arnon) 320:7-16.) At that point, however, she and her colleagues had no idea what was causing the side effects or how they could get rid of them. (July Tr. (Arnon) 320:7-16.)

147. Based on the reports from Dr. Bornstein, Professor Arnon and her colleagues looked for screening assays that could be used to differentiate between batches that would cause side effects and those that would not. (July Tr. (Arnon) 320:17-25.) They eventually employed the *in vitro* RBL degranulation test. (July Tr. (Arnon) 320:17-25; DTX 3114.)

148. In the RBL degranulation test, RBL cells are preloaded with radiolabeled serotonin and then exposed to copolymer-1. (July Tr. (Arnon) 327:8-21; July Tr. (Baird) 587:3-589:20.) The amount of serotonin released, or degranulated, by the cells is then measured. (July Tr. (Arnon) 327:8-21; July Tr. (Pinchasi) 25:11-26:1; July Tr. (Baird) 587:3-589:20; DTX 3114.)

149. The RBL test was then (and still is) used as a model for allergic-type reactions, because the degranulation it exhibits in the presence of a stimulant mimics the immune response of human mast cells—a central cell in the allergic immune response system—in responding to allergens or other substances. (July Tr. (Arnon) 321:8-18, 322:21-323:4; July Tr. (Baird) 576:24-577:7, 578:16-582:16, 585:9-21; PTX 522.)

150. The Weizmann scientists adopted the term "toxicity" to refer to the results of the RBL degranulation test. (July Tr. (Arnon) 327:8-21.) If 30% or more serotonin was released upon exposure to copolymer-1, the batch was designated "toxic" and discarded. (July Tr. (Arnon) 327:8-330:18; PTX 31 at 409.)

151. The RBL degranulation test was suggested to Professor Arnon by one of her colleagues at the Weizmann Institute who was very experienced with the test. (July Tr. (Arnon) 321:8-18.)

152. Before making the decision to go forward with the RBL degranulation test, however, Professor Arnon personally read all the literature about the test, including articles by Dr. Reuben Siraganian's group at NIH. (July Tr. (Arnon) 321:8-18, 322:21-323:4; July Tr. (Baird) 576:24-577:7, 578:16-582:16, 585:9-21; PTX 522.)

E. Teva's Development of Copolymer-1 with the Weizmann Institute

153. In November 1987, Teva and Yeda, the commercial arm of the Weizmann Institute, entered into an agreement for the development of copolymer-1. (DTX 1232.) Teva's goal was to take the invention made by the Weizmann Institute scientists and translate it into a useful pharmaceutical product that could be given to multiple sclerosis patients. (July Tr. (Pinchasi) 12:10-16.)

154. The copolymer-1 project at Teva was divided into chemical, analytical, pharmaceutical and biological development teams, which were responsible for different aspects of the project. (July Tr. (Pinchasi) 15:4-18.)

155. Dr. Irit Pinchasi served as project manager of the copolymer-1 project at Teva, and was responsible for coordinating all development work. (July Tr. (Pinchasi) 11:6-12, 14:12-15:3.)

156. Because Dr. Pinchasi is not a chemist, she had only high-level managerial responsibility for the chemical, analytical and pharmaceutical aspects of the project. (July Tr. (Pinchasi) 15:4-16:3.) She had more substantive input into the biological aspects of the project. (July Tr. (Pinchasi) 14:12-16:3.)

157. The biology team consisted of Dr. Pinchasi at Teva and Professor Arnon and Dr. Teitelbaum at the Weizmann Institute. (July Tr. (Pinchasi) 16:4-18.) Dr. Pinchasi met frequently with both Professor Arnon and Dr. Teitelbaum, and worked in Dr. Teitelbaum's lab for several months. (July Tr. (Pinchasi) 16:19-17:5.) Although Professor Arnon was involved at a higher level, she was consulted on all significant decisions. (July Tr. (Pinchasi) 16:19-17:5.)

158. When Dr. Pinchasi began working on the project, she understood from the Weizmann Institute scientists that copolymer-1 needed to have a molecular weight in the range of MBP, which was about 20,000 daltons. (July Tr. (Pinchasi) 18:6-19:1, 33:6-20.)

159. In fact, in 1974, Professor Arnon and her colleagues had published an abstract in the Israeli Journal of Medical Sciences ("1974 Teitelbaum abstract") that reported that copolymers having the same composition as copolymer-1 but with molecular weights lower than 17,000 or higher than 50,000 daltons proved ineffective for suppression of EAE. (July Tr. (Arnon) 312:23-313:18; Sept. Tr. (Grant) 1442:8-1444:4; PTX 509 at 1172-73.)

160. Dr. Pinchasi also learned that the molecular weight of the copolymer-1 used in the Bornstein trial was 14,000 to 23,000 daltons. (July Tr. (Pinchasi) 22:4-21, 33:21-34:5.)

161. Teva therefore aimed at that time to produce a high molecular weight copolymer-1, in the range of 20,000 daltons. (July Tr. (Pinchasi) 18:6-19:1, 33:6-34:5.)

F. The Discovery of the Correlation Between Molecular Weight and Toxicity

162. At the beginning of the copolymer-1 project, Dr. Pinchasi and her team were informed about the local and systemic side effects that Dr. Bornstein had seen in his clinical trial.

(July Tr. (Pinchasi) 24:2-23.) They learned that the Weizmann Institute scientists had concluded that these side effects were caused by something "toxic" in the copolymer-1 batches, but that Professor Arnon and her colleagues had no idea what that toxic element was. (July Tr. (Pinchasi) 24:24-25:10.) Dr. Pinchasi and her team also learned that the Weizmann Institute scientists had developed the RBL degranulation test in order to screen batches for "toxicity." (July Tr. (Pinchasi) 25:11-26:18.)

163. Solving the toxicity problem was one of the major challenges that the Teva and Weizmann Institute scientists initially faced in developing copolymer-1 into a pharmaceutical product, and much of their development work was focused on this issue. (July Tr. (Pinchasi) 26:19-27:6; July Tr. (Arnon) 331:7-333:6.)

164. The Teva and Weizmann Institute scientists studied the literature for clues as to what might be causing the toxicity, and investigated many different possibilities. (July Tr. (Pinchasi) 26:19-27:6.) In the end, the literature did not provide an answer. (July Tr. (Pinchasi) 26:19-27:19.)

165. Finally, the Teva and Weizmann Institute scientists discovered, to their surprise, that toxicity was related to the molecular weight of the product. (July Tr. (Pinchasi) 27:25-28:25.) The higher the average molecular weight of a copolymer-1 batch, the higher the probability that the batch will be toxic. (July Tr. (Pinchasi) 27:25-28:25; July Tr. (Arnon) 332:8-333:6; DTX 3567 (Konfino Dep. Tr. Vol. 1) at 62:24-63:9.)

166. In particular, they discovered that there was a narrow molecular weight range between 5,000 and 9,000 daltons in which there is a high probability that a copolymer-1 batch will be both active and non-toxic. (July Tr. (Arnon) 333:7-17; July Tr. (Pinchasi) 34:6-35:5.)

167. Teva initially determined toxicity using the Weizmann Institute's RBL

degranulation test. (July Tr. (Pinchasi) 29:1-5.) Teva later added an *in vivo* toxicity test in which copolymer-1 is injected into mice. (July Tr. (Pinchasi) 29:1-13.)

168. The correlation between molecular weight and toxicity that was discovered by the Teva and Weizmann Institute scientists was very unexpected. (July Tr. (Pinchasi) 32:1-6, 34:19-35:5; July Tr. (Arnon) 333:23-334:2.) There was nothing in the literature that indicated such a correlation. (July Tr. (Pinchasi) 32:1-6.)

169. It was also unexpected that copolymer-1 in the range of 5,000 to 9,000 daltons would be both non-toxic and active. The Weizmann Institute and Teva scientists believed that a much higher molecular weight would be needed in order for copolymer-1 to have activity because copolymer-1 was meant to mimic MBP, with a molecular weight in the range of 20,000 daltons, and because testing by the Weizmann Institute had previously shown lower molecular weight copolymer-1 to be ineffective. (July Tr. (Pinchasi) 33:6-34:5, 34:19-35:5; July Tr. (Arnon) 312:23-313:18, 316:25-317:11, 333:18-22.)

G. Development of Low Molecular Weight Copolymer-1

170. The discovery of the narrow window between 5,000 and 9,000 daltons that would provide active, non-toxic copolymer-1 product was not a welcome one for Teva, as it presented both regulatory and practical challenges. (July Tr. (Pinchasi) 35:12-18, 38:14-39:4, 42:14-24; PTX 41.)

171. From a regulatory perspective, Teva needed to submit to the FDA two pivotal studies on copolymer-1 in order to obtain regulatory approval to market the product in the United States. The two pivotal studies are supposed to be performed with exactly the same product, having exactly the same characteristics. (July Tr. (Pinchasi) 35:12-36:20, 37:18-38:4.)

172. Teva had planned to rely on the Bornstein trial as one of its two pivotal studies. The Bornstein trial, however, used copolymer-1 having a molecular weight between 14,000 and 23,000 daltons. (July Tr. (Pinchasi) 35:18-21, 37:2-14.) Because of the toxicity issues that had been discovered, Teva knew it would have to perform its second pivotal study with much lower molecular weight copolymer-1. Teva understood that the FDA might not accept the Bornstein trial as one of the two pivotal studies if it switched to the lower molecular weight copolymer-1, and that it might therefore have to perform a second trial before copolymer-1 would be approved. (July Tr. (Pinchasi) 37:15-38:4.)

173. From a practical perspective, Teva understood that it would be a challenge to reproducibly produce copolymer-1 having a molecular weight of 5,000 to 9,000 daltons, because the Teva and Weizmann Institute scientists had not yet developed a manufacturing process that could sufficiently control the molecular weight of the final product. (July Tr. (Pinchasi) 38:14-39:4.)

174. Notwithstanding these significant challenges, Teva decided that it could not market a product that had a chance of being toxic, so it targeted a molecular weight for copolymer-1 of about 7,000 daltons. (July Tr. (Pinchasi) 38:5-39:4, 81:13-82:19; PTX 708 at TEV000324552.)

175. Teva's second pivotal trial began in October 1991. (Sept. Tr. (Lisak) 106:24-108:17; PTX 597 at 1271.) This clinical trial, named the Johnson Study after principal investigator Kenneth Johnson, was a Phase III large-scale, multicenter, placebo-controlled, double-blinded study. (Sept. Tr. (Lisak) 106:24-108:17; PTX 597 at 1268.) A total of 251 patients participated in the two-year trial. (Sept. Tr. (Lisak) 106:24-108:17; PTX 597.)

176. The Johnson Study demonstrated for the first time that copolymer-1 was a safe

and effective treatment for patients with RRMS. (Sept. Tr. (Lisak) 110:22-111:22.) The Johnson trial demonstrated, *inter alia*, that daily injections of copolymer-1 resulted in a statistically significant reduction in relapse rates for patients with RRMS. (Sept. Tr. (Lisak) 107:25-108:4; PTX 597 at 1268.) The study concluded in 1994 and the results were published in 1995 in the Journal of Neurology. (PTX 597.)

177. On June 14, 1995, Teva submitted its NDA, relying on both the 1987. Bornstein trial and the Johnson Study to demonstrate the safety and efficacy of copolymer-1. (PTX 81 at TEV000002326.) While Teva represented to the FDA that the safety of the copolymer-1 compositions studied in the Johnson Study and the Bornstein trial were comparable, Teva did not draw any comparisons between the tolerability of the compositions or their propensity to cause injection site reactions. (PTX 881 (Green Dep.) at 111:11-18; PTX 81.)

178. Although Teva's NDA set an average molecular weight specification of 4,700 to 13,000 daltons, Teva actually targeted an average molecular weight of 7,000±1,000 daltons for the batches of copolymer-1 that were to be marketed. (July Tr. (Pinchasi) 85:23-89:22.) Teva informed the FDA of this 7,000±1,000 daltons average molecular weight target as part of its NDA submission. (July Tr. (Pinchasi) 85:23-89:22; DTX 1023 at TEV000000455; *see also* July Tr. (Pinchasi) 81:23-85:13; PTX 723 at TEV000599260.)

179. Teva set the formal specification at 4,700 to 13,000 daltons originally to maintain a larger margin for average molecular weight in light of potential manufacturing changes that might be necessary to market the product. (July Tr. (Pinchasi) 86:4-86:24.) Batches within the 4,700 to 13,000 daltons specification were still tested for toxicity on the RBL screen and *in-vivo* mouse test and rejected if they failed on either of those screens. (July Tr. (Pinchasi) 86:4-24.)

H. Teva's Later Work on TV-5010

180. The discovery by the Teva and Weizmann Institute scientists that toxicity was

correlated with molecular weight was confirmed years later in connection with Teva's TV-5010 project.

181. Years after Copaxone® was introduced to the market, Teva contemplated developing a high molecular weight copolymer-1 that would be administered as a once-weekly injection. The internal Teva name for this high molecular weight copolymer-1 was TV-5010. (July Tr. (Pinchasi) 104:21-105:6.)

182. Teva's hypothesis at the time was that if you gave the high molecular weight copolymer-1 to patients on a once-weekly basis, rather than on a daily basis as Copaxone® is administered, it could compensate for the toxicity issues. (July Tr. (Pinchasi) 105:14-24.)

183. Teva was never able to put the high molecular weight TV-5010 on the market, however, because severe safety issues were discovered during toxicology studies in animals, which included mortality, severe injection site lesions and systemic effects. (July Tr. (Pinchasi) 105:25-111:9; PTX 158.)

I. The Discovery of a Process for Reproducibly Achieving Low Molecular Weight Copolymer-1

184. Teva was able to reproducibly achieve the narrow molecular weight range of about 7,000 daltons because of a discovery made by Teva chemist Eliezer Konfino.

185. When Teva scientists began working on the copolymer-1 project, they found that the same starting materials and what they believed to be the same reaction conditions produced copolymer-1 of varying molecular weights. (July Tr. (Pinchasi) 38:14-39:4.)

186. Mr. Konfino made the unexpected discovery that the second step of the process for making copolymer-1, which involves the addition of HBr/acetic acid, cleaves, or cuts up, the polypeptide copolymer-1 chains, and therefore lowers the average molecular weight of the product. (July Tr. (Pinchasi) 68:5-25, 76:13-77:18, 81:23-85:13; PTX 36; PTX 36-T; PTX 42.)

187. Mr. Konfino found that he could control the average molecular weight of the final copolymer-1 product by controlling the time and temperature of the second step of the process. The longer the reaction is run, and the higher the temperature, the more cleavage occurs and the lower the average molecular weight of the product. (July Tr. (Pinchasi) 68:5-25, 76:13-77:18, 81:23-85:13; PTX 36; PTX 36-T; PTX 42.)

188. Mr. Konfino also discovered that the time and temperature for the Step 2 reaction that would provide copolymer-1 of approximately 7,000 daltons could be determined by running a test reaction. (July Tr. (Pinchasi) 81:23-82:19.)

IV. BACKGROUND ON POLYPEPTIDE CHEMISTRY, SYNTHESIS AND ANALYTICAL TESTING

A. Polypeptide Chemistry

189. A polymer is a molecule composed of smaller subparts called monomers. (Sept. Tr. (Grant) 191:9-16; PTX 986 at 4.) A copolymer is a polymer composed of more than one type of monomer. (Sept. Tr. (Grant) 191:19-192:1; PTX 986 at 4.)

190. The monomers that make up copolymer-1 are amino acids. (Sept. Tr. (Grant) 192:2-3.) An amino acid is a molecule that contains an amino group, a carboxylic acid group, and a side chain. (Sept. Tr. (Grant) 192:4-19; Sept. Tr. (Gokel) 341:6-25; PTX 986 at 5; PTX 987 at 4.)

191. A polypeptide is a molecule made up of amino acid monomers that are joined together by peptide bonds. (Sept. Tr. (Grant) 180:17-21; Sept. Tr. (Gokel) 344:11-22.) Copolymer-1 is a mixture of polypeptides. (PTX 1, col. 1:32.)

192. The polypeptides comprising copolymer-1 are synthetic – meaning that they are made in a laboratory – and they are composed of four amino acids: glutamic acid, lysine, alanine, and tyrosine. (Sept. Tr. (Grant) 180:22-23, 183:13-19, 192:20-193:23; Sept. Tr. (Gokel) 342:12-

344:10, 344:23-345:12; PTX 986 at 6-7; PTX 987 at 6, 8-11.)

193. The individual polypeptide molecules, or "species," in copolymer-1 have different lengths and sequences. For that reason, the molecular weight of a sample of copolymer-1 can best be described either as an average molecular weight or as a molecular weight distribution. (Sept. Tr. (Grant) 194:14-195:2, 195:7-10, 1544:23-1545:11; Sept. Tr. (Scandella) 1193:24-1194:2; PTX 986 at 8.)

194. The molecular weight of an individual polypeptide molecule is the sum of the atomic weights of the atoms comprising the molecule. (Sept. Tr. (Grant) 193:24-194:13.) A molecular weight distribution, by contrast, is a description of the molecular weights of the polypeptides that make up a mixture of polypeptide molecules. (Sept. Tr. (Grant) 198:9-13.)

B. Synthesis of Copolymer-1

195. The varying lengths and sequences of the polypeptide chains in a sample of copolymer-1 are a result of the method of its synthesis. (Sept. Tr. (Grant) 195:11-197:10.)

196. The patents-in-suit teach that copolymer-1 is synthesized using a four-step process in a "batch" method of synthesis. (Sept. Tr. (Gokel) 352:2-354:15; Sept. Tr. (Grant) 1401:19-1402:4; PTX 1, col. 4:30-col. 6:3; PTX 987 at 22.)

197. In Step 1, the N-carboxyanhydrides, or activated versions, of the amino acids glutamic acid, lysine, alanine, and tyrosine are combined in the presence of a chemical called an initiator. The initiator starts the reaction of the amino acids by joining with one of the activated amino acids, which removes the N-carboxyanhydride group and allows the first amino acid to join to a second amino acid, which in turn allows the second amino acid to react with a third amino acid, and so forth. Each initiator molecule starts a new polypeptide chain. This sequence of reactions results in polymerization of the amino acids into polypeptide chains. (Sept. Tr. (Grant) 195:17-197:16; Sept. Tr. (Gokel) 349:3; PTX 986 at 9; PTX 987 at 14.)

198. Glutamic acid and lysine each have two sites that can form bonds with other amino acids. In order to ensure that the amino acids combine with each other in a straight chain and do not become branched during the polymerization step, protecting groups are used to block the reactive sites on the side chain of each of these amino acids. Benzyl groups are used to protect the glutamic acid and TFA groups are used to protect the lysine. (Sept. Tr. (Gokel) 342:16-343:23, 345:5-346:25; PTX 987 at 7, 12-13.)

199. The result of the Step 1 polymerization is called "protected copolymer-1" because the side chains of glutamic acid and lysine are protected by the benzyl and TFA protecting groups, respectively. Protected copolymer-1 is a mixture of polypeptides that have different lengths and amino acid sequences. (Sept. Tr. (Grant) 195:17-197:16; Sept. Tr. (Gokel) 347:1-349:8, 353:4-16; PTX 987 at 15, 22.)

200. In Step 2, the protected copolymer-1 is treated with HBr/acetic acid to remove the benzyl protecting groups from glutamic acids (deprotection). During this deprotection process, the polypeptide chains are also cleaved (depolymerized), which results in shorter polypeptide chains. (Sept. Tr. (Gokel) 347:1-350:5, 353:17-25; PTX 987 at 16-18, 22.) The resulting product of the Step 2 (deprotection/depolymerization) is called TFA copolymer-1 because the TFA protecting groups remain on the lysine residues. (Sept. Tr. (Gokel) 350:11-18.)

201. The time and temperature of the HBr/acetic acid reaction of Step 2 determines the extent of cleavage of the polypeptide chains and the resulting average molecular weight of the copolymer-1 product. (PTX 1, col. 4:59-65.) The longer the reaction is run or the higher the temperature, the more cleavage occurs and the lower the average molecular weight of the product. This step is therefore used to control the molecular weight of the resulting copolymer-

1. (Sept. Tr. (Sampson) 1641:6-1642:8; PTX 992 at 6-7; July Tr. (Pinchasi) 81:23-82:19; DTX 1023 at TEV000000455.)

202. In Step 3 of the synthetic process, the TFA copolymer-1 is treated with piperidine to remove the TFA protecting groups from the lysines, resulting in copolymer-1. (Sept. Tr. (Gokel) 350:19-22, 351:3-12, 354:1-9; PTX 987 at 15, 22.) The chain lengths of the polypeptides are not affected in the TFA deprotection step. (Sept. Tr. (Gokel) 350:23-351:2.)

203. In Step 4 of the synthetic process, the copolymer-1 can be purified by dialysis. In one method of dialysis, acetic acid is used. (Sept. Tr. (Gokel) 350:23-351:2; PTX 1, col. 5:12-col. 6:2; PTX 987 at 22.)

C. Size Exclusion Chromatography

204. The patents-in-suit explicitly identify size exclusion chromatography ("SEC") as the method to be used for determining the molecular weight of copolymer-1. (Sept. Tr. (Grant) 186:16-20, 197:17-25, 326:15-18; Sept. Tr. (Scandella) 1227:5-10; PTX 1, col. 3:6-7.)

205. SEC, otherwise known as "gel filtration" or "gel permeation chromatography," is a separation and analytical technique that separates molecules based upon their size in solution. SEC can be used to determine the molecular weights of samples, such as polypeptides, as well as their molecular weight distributions. (Sept. Tr. (Grant) 186:5-15, 186:21-187:4, 198:1-3, 198:14-20, 329:14-20, 1411:2-5, 1415:8-17; PTX 553 at 63, last line-64, line 4; PTX 566 at 2, lines 5-7.)

206. SEC was first described in the literature in the late 1950s or early 1960s, and the first commercial SEC instrument was marketed in 1964. (Sept. Tr. (Grant) 1409:17-19; PTX 553 at 63-64; PTX 514 at 199.)

207. By 1994 there was a huge volume of scientific literature describing the use of SEC. (Sept. Tr. (Grant) 1409:17-23; Sept. Tr. (Scandella) 1314:15-25.) This literature included

textbooks, individual book chapters, and numerous scientific articles. (Sept. Tr. (Grant) 1409:24-1410:2.) For example, N.C. Billingham, Molar Mass Measurements in Polymer Science (John Wiley & Sons 1977) ("Billingham 1977"), contains a chapter entitled "Gel Permeation Chromatography," which states that "[t]he idea of producing separation of discrete molecular species on the basis of differences in molecular size has been familiar to the biochemist for many years." (PTX 514 at 199.)

208. Polypeptides were some of the first substances studied by SEC, and by 1994, the prior art with respect to using SEC to determine the molecular weight of polypeptides was extensive. (Sept. Tr. (Grant) 1410:3-9.)

209. By 1994, all aspects of the SEC process—including its theory and practice, and the interpretation of results—had been described in numerous book chapters such as Billingham 1977, the "Gel Filtration" chapter in Protein Purification – Principles, High Resolution Methods and Applications (Jan-Christer Janson and Lars Ryden eds., 1989) ("Janson 1989"), and the "Characterization of Complex Polymers by Size Exclusion Chromatography and High-Performance Liquid Chromatography" chapter from Modern Methods of Polymer Characterization (Howard G. Barth and Jimmy W. Mays, 1991) ("Barth 1991"). (Sept. Tr. (Grant) 1410:10-1412:5, 1414:8-21, 1418:19-1419:21; PTX 514; PTX 553; PTX 566.)

210. SEC was in 1994—and still is—the best way of determining the molecular weight distribution of a mixture of polypeptides like copolymer-1. For example, Barth 1991 describes SEC as "a well-recognized technique for the determination of polymer molecular weight distributions." (PTX 566 at 2.) In addition, Billingham 1977 explains that SEC is "used as a matter of routine in very many polymer laboratories" to characterize the molecular weight of polydisperse polymers. (Sept. Tr. (Grant) 198:14-20, 329:14-20; PTX 514 at 200.)

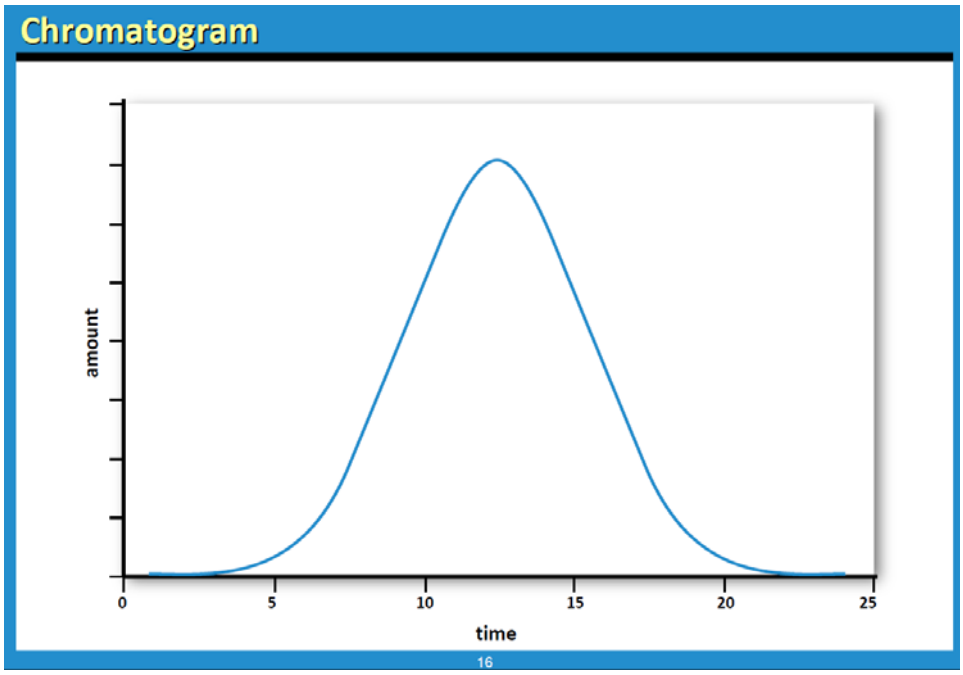
211. SEC analysis utilizes a size exclusion (or gel filtration) column, which is a gel-filled glass or metal cylinder where the separation of molecules takes place. (Sept. Tr. (Grant) 198:4-8, 198:24-199:25; PTX 986 at 10-11.)

212. The sample to be analyzed is introduced into the top of the column along with liquid which carries the sample down through the gel. (Sept. Tr. (Grant) 200:1-13; PTX 986 at 12-13.) The individual beads making up the separation gel have many pores of varying sizes. Size exclusion takes place because large molecules cannot get into the pores, and therefore pass through quickly, while smaller molecules can go into the pores to various extents, and therefore travel a longer path through the column and come out later than the larger molecules. (Sept. Tr. (Grant) 199:12-25, 200:14-201:7; PTX 986 at 14-15.) For this reason, molecules of different sizes are separated from one another as they travel through the column.

213. The bottom of the column is connected through a tube to a detector, which detects the presence and the quantity (amount) of molecules exiting the column. (Sept. Tr. (Grant) 201:8-24.)

214. The output of the detector is a graph, called a chromatogram, which is plotted on the x-axis as time and on the y-axis as the amount of the material passing the detector at each point in time. (Sept. Tr. (Grant) 201:25-203:19; PTX 986 at 16.) Larger molecules exit the column first due to the size exclusion. (Sept. Tr. (Grant) 200:23-201:7; PTX 986 at 13.) The highest point, or peak, of the chromatogram, represents the time at which the species of molecules present in the highest abundance pass by the detector. (Sept. Tr. (Grant) 1404:23-1405:9; PTX 969 (Svec Dep.) at 9:19-23; PTX 982.)

Figure 1



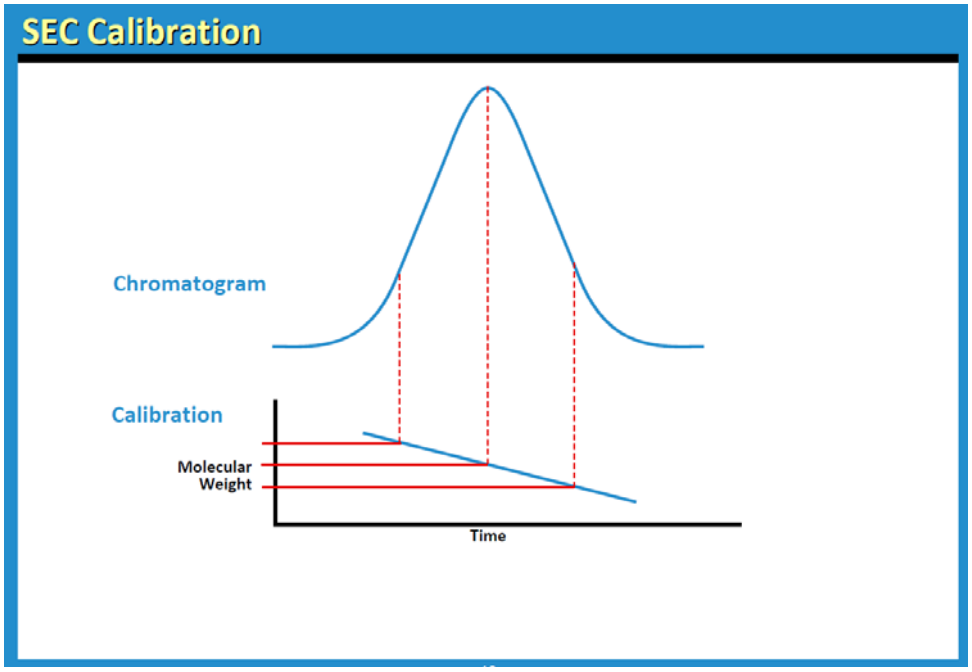
(PTX 986 at 16.)

215. In order to determine the molecular weight of the molecules exiting the column at each point (or time) along the chromatogram, it is necessary to have a calibration curve, which correlates the time at each point along the chromatogram's x-axis with the molecular weight of material exiting the column at that particular time. (Sept. Tr. (Grant) 203:20-204:3.)

216. SEC calibration was well-understood in 1994. (Sept. Tr. (Grant) 204:4-5.) By that time, it was well-known in 1994 that to create a calibration curve, calibration standards—molecules of known molecular weights—had to be run through the column to determine the time that they exited the SEC apparatus. The molecular weight of each standard, which can be determined by a number of independent (non-SEC) methods, is plotted against the time the standard comes out of the column. (Sept. Tr. (Grant) 204:6-205:10; PTX 986 at 17.)

217. To determine the molecular weight at any point (*e.g.*, the peak) on the chromatogram, one can match the time from the x-axis to the corresponding time on the calibration curve and read the molecular weight from the y-axis of the calibration curve. (Sept. Tr. (Grant) 205:11-206:2; PTX 986 at 18.)

Figure 2



218. It was known in 1994 that there were at least two options for calibrating an SEC column to get accurate molecular weights for a polypeptide mixture like copolymer-1: the conventional way was to use calibration standards that have the same relationship between size and shape in solution (also known as "hydrodynamic volume") and molecular weight as the sample being measured, and the other was to use a method called "universal calibration." (Sept. Tr. (Grant) 206:3-208:20, 1399:18-1400:13; PTX 969 (Svec Dep.) at 94:21-95:5; PTX 990 at 2.)

219. The necessity of matching the hydrodynamic characteristics of the sample and the calibration standards in conventional SEC calibration was well-known to those of skill in the art and well-described in the literature in 1994. (Sept. Tr. (Grant) 1412:6-1413:16; Sept. Tr.

(Scandella) 1314:15-1316:24; PTX 961 (Kota Dep.) at 18:3-14; PTX 962 (B. Rao Dep.) at 75:6-76:10, 78:14-80:5; PTX 973 (Venkataraman Dep) at 108:20-109:23; PTX 974 (Wallingford Dep.) at 146:9-149:7; PTX 317 at MYL0000111; PTX 553 at 72.) For example, Janson 1989 states that "[t]he relationship between size and molecular weight of solutes is strongly dependent upon solute shape. . . . It is readily seen that calibration versus molecular weight is only meaningful for solutes of similar shape." (PTX 553 at 72.)

220. On the other hand, if standards that match the hydrodynamic volume to molecular weight characteristics of the sample were unavailable, it was also well known that universal calibration could be used to determine an accurate molecular weight for a sample. (Sept. Tr. (Grant) 208:14-20, 1399:18-1400:13, 1401:12-18, 1413:17-23; PTX 970 (Svec Dep.) at 320:2-321:10, 326:14-327:10.)

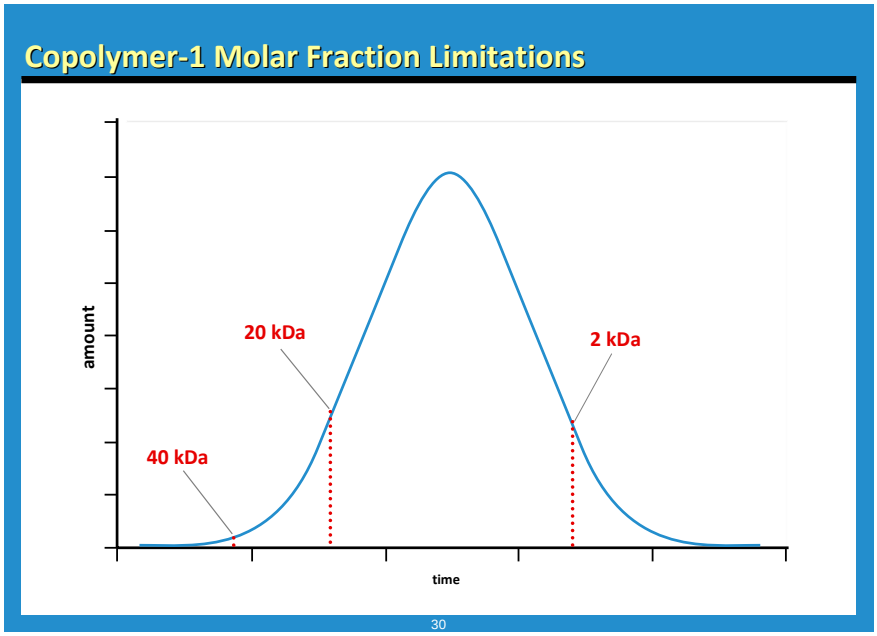
221. Universal calibration does not require the standards to have the same hydrodynamic volume to molecular weight relationship as the sample, because it uses a different physical property (intrinsic viscosity) to allow a correlation of the size of molecules exiting the column to their molecular weight. (Sept. Tr. (Grant) 208:14-20, 1400:6-15.)

222. In addition to allowing determination of an average molecular weight, SEC allows the separation of molecules and the determination of the percentage of molecules having molecular weights falling within any given molecular weight range. (Sept. Tr. (Grant) 209:17-25, 227:8-22; PTX 986 at 33.)

223. A chromatogram represents the amount of material that is exiting the size exclusion column at any particular time (as reflected on the x-axis). The chromatogram represents the entirety of the molecules in the sample. (Sept. Tr. (Grant) 203:14-19.) On the illustrative chromatogram shown below, the molecular weights of 40 kDa, 20 kDa, and 2kDa are

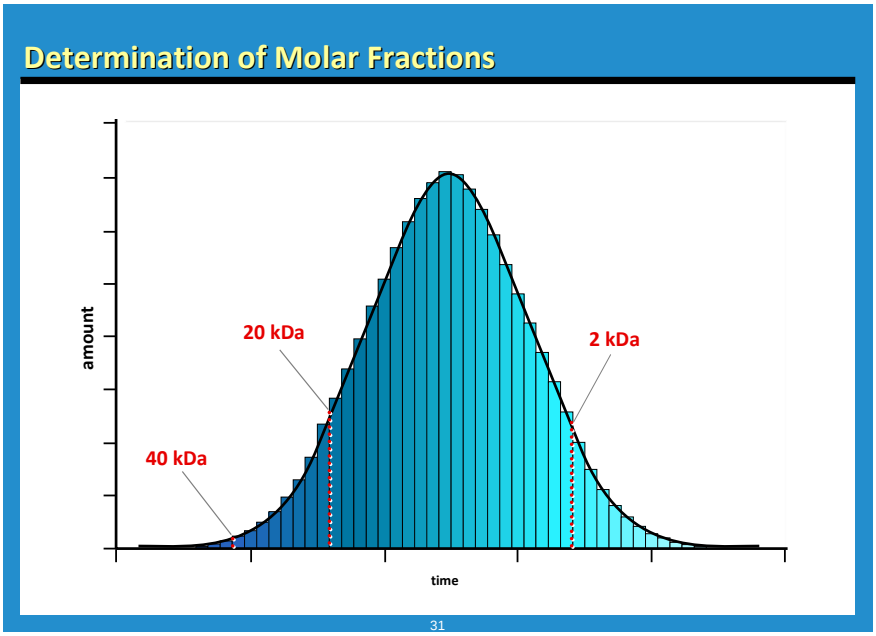
depicted from left to right because large molecules come out of the size exclusion column earlier than smaller molecules. (Sept. Tr. (Grant) 227:8-22; PTX 986 at 30.)

Figure 3



224. In order to calculate the percentage of species having a molecular weight within a certain range, the chromatogram is divided into slices, which can be represented by small rectangles, as shown in the figure below. A molecular weight is assigned to each slice through the use of a calibration curve. The number of moles of the material, which represents the number of molecules, in each slice can be calculated by dividing the amount of the material in the slice by the molecular weight that has been assigned to that slice. (Sept. Tr. (Grant) 228:11-229:11, 230:8-12; PTX 986 at 31.)

Figure 4



225. The number of moles (*i.e.*, the number of molecules) of all of the molecules falling within a molecular weight range, *e.g.*, between 2 kDa and 20 kDa, can be added together and divided by the total number of moles of all of the molecules present in the sample, as represented by the entire chromatogram. Multiplying this fraction by 100 gives the percentage (on a "molar fraction" basis) of molecules within the molecular weight range. Similarly, the molar percentage of molecules having molecular weights of above 40 kDa can be calculated by dividing the number of moles of material having molecular weight of above 40 kDa by the total number of moles of the materials represented by the entire chromatogram. (Sept. Tr. (Grant) 229:12-230:7; PTX 986 at 32.)

226. When using this method, it is not necessary to know how many different molecular weights are in each slice. It is acceptable to assign a single molecular weight to each slice. (Sept. Tr. (Grant) 298:11-299:3, 329:6-330:7; PTX 986 at 31.)

V. LEVEL OF ORDINARY SKILL IN THE ART

227. Dr. Grant has defined a person of ordinary skill in the art as having an "advanced degree or equivalent in a chemical or biological discipline and significant experience in the synthesis or characterization of polymers, including proteins or synthetic peptides." The person of ordinary skill in the art also "has access to and the ability to consult with other scientists having related and/or complementary knowledge and experience in the areas of polymer chemistry, biochemistry, analytical chemistry, separation technology, medicine, and toxicology." (Sept. Tr. (Grant) 189:19-190:6, 1398:11-17; PTX 986 at 3.)

228. Defendants' expert witnesses have similarly defined the level of skill in the art as being high. (Sept. Tr. (Scandella) 1190:15-20, 1300:20-1301:9; Sept. Tr. (Wall) 1756:2-12; Sept. Tr. (Zeiger) 809:10-811:15; DTX 4030 at 4.)

229. For example, Sandoz's expert Dr. Scandella defined a person of ordinary skill in the art as having a Ph.D. in chemistry, biochemistry or related field with a minimum of three years of experience in chromatography, and specifically in size exclusion chromatography of macromolecules. (Sept. Tr. (Scandella) 1190:15-20, 1300:20-1301:9.)

230. Sandoz's expert Dr. Wall defined a person of ordinary skill in the art as having a Ph.D. in chemistry or biochemistry or related field with three years of experience in chromatography or a person who has supervised or directed a research lab that conducts chromatography. (Sept. Tr. (Wall) 1756:2-12.)

231. Mylan's expert Dr. Zeiger testified that he has "no problem" with Dr. Grant's definition of a person of ordinary skill in the art. (Sept. Tr. (Zeiger) 811:15.) Dr. Zeiger himself defined a person of ordinary skill as: "A person of ordinary skill in fields of biochemistry and immunology in 1994 would have had an advanced degree in a chemical or biological discipline, and extensive experience in the synthesis, fractionation, and characterization of polymers, such

as their hydrodynamic and structural properties, as applied to proteins, synthetic peptides and/or polydisperse peptide mixtures, as well as experience in the determination of the molecular weight distribution and average molecular weights of such polymers by methods such as size exclusion chromatography (SEC), and an understanding of how the standards and conditions used in the molecular weight determination affect the results obtained." (Sept. Tr. (Zeiger) 809:10-811:15; DTX 4030 at 4.)

232. The Court credits Dr. Grant's testimony and adopts his proposed definition of the level of ordinary skill in the art. Nonetheless, in light of the nearly identical view of the level of ordinary skill in the art put forward by the parties' experts, the Court's analysis of the legal and factual issues, as set forth below, is the same regardless of which definition is used.

VI. FINDINGS OF FACT AND CONCLUSIONS OF LAW RELATING TO INFRINGEMENT

233. Plaintiffs presented evidence at trial that Defendants' proposed products meets each and every limitation of the asserted claims. Mylan largely does not contest infringement, with the exception of its assertion that its product is not "copolymer-1." Sandoz similarly does not contest that its proposed product meets almost every limitation of the asserted claims. Sandoz asserts only that its product is not "copolymer-1" and that the process [redacted] does not include in Step 2 a time "predetermined by a test reaction." Sandoz's claim that its product is not copolymer-1 was made for the first time on the eve of trial, and Sandoz proffered no evidence to support it. Sandoz does not dispute that its current ANDA process, and the process in the Briefing Book, should that be proposed and accepted by the FDA, includes a time "predetermined by test reaction." For the reasons set forth below, Mylan's and Sandoz's proposed products infringe each of the asserted claims.

A. Legal Principles

234. A finding of patent infringement is a two-step process. First, the claims must be construed by the court as a matter of law. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) (*en banc*), *aff'd*, 517 U.S. 370 (1996). The inquiry is an objective one. A court must determine "what one of ordinary skill in the art at the time of the invention would have understood the term to mean." *Id.* at 986. On August 29, 2011, the Court issued its claim construction decision, construing the disputed claim terms. (D.I. 275.) The Court will apply its prior construction of each claim term to determine infringement, as set forth below.

235. Second, the construed claims must be compared to the accused product or process to determine whether all of the limitations of at least one claim are present, either literally or by an equivalent. *Acumed LLC v. Stryker Corp.*, 483 F.3d 800, 804 (Fed. Cir. 2007) (citing *Markman*, 52 F.3d at 976); *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1323 (Fed. Cir. 2002).

236. The doctrine of equivalents prevents an accused infringer from avoiding claim limitations by making minor or insubstantial changes to the accused product to avoid infringement while retaining the identity of the invention. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 234 F.3d 558, 564 (Fed. Cir. 2000), *vacated on other grounds by* 535 U.S. 722 (2002). This Court has noted that the doctrine of equivalents is used to "temper unsparing logic and prevent an infringer from stealing the benefit of the invention." *Astra Aktiebolag v. Andrx Pharms., Inc.*, 222 F. Supp. 2d 423, 504 (S.D.N.Y. 2002) (quoting *Festo*, 234 F.3d at 564 (Fed. Cir. 2000)). An accused product infringes under the doctrine of equivalents if the limitations of the claim are insubstantially different from the accused product. *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1351 (Fed. Cir. 2003); *Eagle Comtronics v. Arrow Commc'n Labs.*, 305 F.3d 1303, 1315 (Fed. Cir. 2002).

237. Pursuant to 35 U.S.C. § 271(b), "[w]hoever actively induces infringement of a patent shall be liable as an infringer." To establish a claim of induced infringement, a patentee must show by the preponderance of the evidence that the accused infringer knowingly induced infringement and had a specifc intent to encourage another's infringement. *E.g., AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1056 (Fed. Cir. 2010).

238. Infringement must be shown by a preponderance of the evidence, which requires showing that it is more likely than not that infringement has occurred. *See Enercon GmbH v. ITC*, 151 F.3d 1376, 1384 (Fed. Cir. 1998); *In re Omeprazole Patent Litig.*, 490 F. Supp. 2d 381, 414 (S.D.N.Y. 2007).

B. Findings of Fact

(i) Mylan's ANDA Product

(1) Active Ingredient

239. The active ingredient in Mylan's proposed product is described as glatiramer acetate. (Sept. Tr. (Owens) 629:1-12; PTX 319 at MYL0000143; PTX 320 at MYL0000235-236; PTX 962 (B. Rao 06/09/2010 Dep.) at 37:14-2; PTX 984 at 1.) Mylan's ANDA makes clear in several places, however, that glatiramer acetate was formerly known as, and is synonymous with, "copolymer-1." For example, copolymer-1 is listed in the Nomenclature section of the ANDA as a "synonym" for glatiramer acetate. (Sept. Tr. (Grant) 250:7-9; Sept. Tr. (Owens) 630:11-631:8; PTX 320 at MYL0000236.) Mylan's proposed labeling also states that glatiramer acetate was "formerly known as copolymer-1." (Sept. Tr. (Gokel) 369:21-370:3; 372:14-18; 373:14-18; PTX 321 at MYL 0000253; PTX 734 at MYL0004956; PTX 962 (B. Rao 06/09/2010 Dep.) at 192:6-10; PTX 987 at 55.) In addition, the Manufacturing section of the ANDA refers to the product of Mylan's manufacturing process as "copolymer-1." (PTX 321 at MYL0000253, 622.)

240. Natco scientists have also acknowledged that Mylan's proposed product is copolymer-1. Dr. Bhujanga Rao, who is the President of Research & Development at Natco and was Natco's 30(b)(6) witness, testified that the Mylan/Natco proposed product is a "copolymer-1 composition" and that Mylan's scientists understood that the terms "glatiramer acetate" and "copolymer-1" are "used interchangeably." (PTX 962 at 11:13-19, 23:20-24:2, 259:21-260:3.) Dr. Satyanarayana Kota, who is the general manager of Research & Development at Natco and the scientist responsible for starting its peptide group, similarly testified that glatiramer acetate and copolymer-1 are "the same." (PTX 961 (Kota Dep.) at 28:1-16, 52:17-53:8, 202:15-25.)

(a) Amino Acid Composition

241. The glatiramer acetate in Mylan's proposed product is composed of the four amino acids glutamic acid, alanine, lysine, and tyrosine. (Sept. Tr. (Gokel) 378:6-14; 394:17-395:2; PTX 320 at MYL0000237, 615-617.) Mylan's ANDA provides the molar fractions for these four amino acids, which represent the relative proportions of the four amino acids in Mylan's product. (Sept. Tr. (Gokel) 380:21-381:14, 394:17-395:22; PTX 325 at MYL0001050, 68, 79; PTX 961 (Kota Dep.) at 71:5-15, 111:25-112:16.)

242. According to Mylan's ANDA, its glatiramer acetate lots have the following molar fractions of glutamic acid, alanine, tyrosine and lysine, respectively: Drug substance lot GMA/001/09, 0.144: 0.427: 0.092: 0.336; Drug substance lot GMA/002/09, 0.148: 0.432: 0.092: 0.328; Drug Substance lot GMA/003/09, 0.142: 0.440: 0.092: 0.327; Drug product lot WV901, 0.137: 0.462: 0.090: 0.311; Drug product lot WV902, 0.146: 0.463: 0.088: 0.304; and Drug product lot WV903, 0.144: 0.464: 0.088: 0.305. (Sept. Tr. (Gokel) 394:17-395:16, 399:20-400:1, 400:4-6; PTX 300 at MYL0002927; PTX 312 at MYL0002929; PTX 313 at MYL0002931; PTX 325 at MYL0001050, 68, 79; PTX 961 (Kota Dep.) at 111:25-112:16.)

(b) Molecular weight

243. Mylan's specification for the peak average molecular weight of its proposed product is between 5,000 and 9,000 daltons. (Sept. Tr. (Grant) 249:21-251:20, 253:25-254:8, 312:1-22, 313:12-22, 314:21-315:3; PTX 300 at MYL0002928; PTX 312 at MYL0002930; PTX 313 at MYL0002932; PTX 318 at MYL00000107, 117; PTX 325 at MYL0001050, 68, 79; PTX 330 at MYL0000752, 765, 766; PTX 986 at 42, 43.)

244. As set forth in Figure 5 below, the data in Mylan's ANDA demonstrate that each of its lots falls within the specified 5,000-9,000 daltons range. (Sept. Tr. (Grant) 249:17-251:20, 255:13-257:11, 257:18-258:3, 258:9-19, 258:25-259:23; PTX 300 at MYL0002928; PTX 312 at MYL0002930; PTX 313 at MYL0002932; PTX 318 at MYL00000107, 117; PTX 325 at MYL0001050, 1068, 179; PTX 986 at 42-44.)

Figure 5

Drug Substance

Lot	Peak Average Molecular Weight (Da)
GMA/001/09	6445
GMA/002/09	6431
GMA/003/09	6718

Drug Product

Batch	Peak Average Molecular Weight (Da)
WV901	6280
WV902	6358
WV903	6036

Source: PTX 300, 312, 313, 325

245. Mylan determined the peak molecular weight values in its ANDA using SEC with a Superose 12 column. (Sept. Tr. (Grant) 252:2-8, 254:12-20; PTX 323 at MYL0000765-66.) Mylan calibrated its SEC column using peptide standards that (i) had amino acid compositions

consistent with the composition of copolymer-1 and (ii) had the same size-to-molecular weight relationship as copolymer-1. (Sept. Tr. (Grant) 250:23-251:7; PTX 323 at MYL0000765-66.)

246. In addition to having a specified peak molecular weight, Mylan's proposed product also has particular molecular weight distribution characteristics. (Sept. Tr. (Grant) 260:23-263:9; PTX 421; PTX 986 at 46.)

247. Dr. Grant used electronic molecular weight data generated by Mylan during its SEC measurements of three Mylan drug substance lots to calculate the percentage (on a molar fraction basis, see paragraph 225 above) of the copolymer-1 molecules in each lot having a molecular weight between 2 and 20 kilodaltons and the percentage having a molecular weight above 40 kilodaltons. (Sept. Tr. (Grant) 260:23-263:9; PTX 421; PTX 986 at 46.) Those percentages are listed in Figure 6 below:

Figure 6

	% molar fraction between 2 and 20 kilodaltons (%)	% molar fraction above 40 kilodaltons (%)
GMA-001-09	≥ 83.13%	≤ 0.03%
GMA-002-09	≥ 81.70%	≤ 0.05%
GMA-003-09	≥ 80.95%	≤ 0.04%

Source: PTX 421

248. Using the electronic molecular weight data for the same three Mylan drug substance lots, Dr. Grant also calculated the molar fraction percentage of molecules having molecular weights between 2 and 20 kilodaltons in the TFA copolymer-1 intermediate that corresponds to each lot. (Sept. Tr. (Grant) 263:22-265:9; PTX 421; PTX 986 at 50.) Those percentages are listed in Figure 7 below:

Figure 7

Trifluoroacetyl copolymer-1 corresponding to sample	% TFA molar fraction between 2 and 20 kilodaltons (%)
GMA-001-09	≥ 87.45
GMA-002-09	≥ 86.09
GMA-003-09	≥ 84.52

Source: PTX 421

249. Mylan criticized Dr. Grant's use of the electronic molecular weight data because it was generated using Mylan's original set of peptide standards as calibration markers. Mylan argued that because of the limited number of standards, the calibration could not be extrapolated beyond the molecular weights of the peptide standards. Dr. Grant explained that such extrapolation was appropriate in this context. (Sept. Tr. (Grant) 319:2-9.) First, Dr. Grant explained that Mylan's molecular weight software had applied the calibration across the entire distribution. (Sept. Tr. (Grant) 318:17-321:5.) Second, using these same data Mylan had itself analyzed the molecular weight distribution of its proposed product and calculated the percentange of molecules having molecular weights between 2 and 20 kilodaltons. Third, Mylan had calculated the weight average and number average molecular weights for its product. All of those calculations required Mylan to extrapolate its calibration beyond the molecular weights of the peptide standards to cover the entire molecular weight distribution. Mylan reported all of this information to the FDA based on its original set of peptide standards. (Sept. Tr. (Grant) 318:12-321:5l; PTX 25 at 1057.) Mylan's argument that such an extrapolation is not appropriate is not credible.

250. During trial, Mylan produced to Plaintiffs additional electronic data for its proposed product generated using SEC with universal calibration. Using this newly-produced data, Dr. Grant performed another set of calculations of the molar fraction percentages for

Mylan's lots. (Sept. Tr. (Grant) 1464:8-1468:4.) Consistent with his previous calculations, Dr. Grant found that, in each of Mylan's lots, greater than 90% of the copolymer-1 molecules on a molar fraction basis had molecular weights between 2 and 20 kilodaltons. (Sept. Tr. (Grant) 1465:16-25.) Dr. Grant also found that, in all lots, less than or equal to 2.5% by molar fraction of the copolymer-1 molecules had molecular weights above 40 kilodaltons. (Sept. Tr. (Grant) 1466:9-19.)

251. Dr. Grant also calculated the molar fraction percentage of molecules having molecular weights between 2 and 20 kilodaltons in the TFA copolymer-1 intermediate that corresponds to each of Mylan's lots based on the universal calibration data produced during trial. (Sept. Tr. (Grant) 1466:1-19.) He found the percentage to be greater than or equal to 90% for all lots. (Sept. Tr. (Grant) 1466:1-8.)

(2) Mylan's Manufacturing Process

(a) Development of Process

252. Natco scientist Dr. Kota was responsible for developing Natco's generic Copaxone® product. (PTX 962 at 26:8-27:4, 35:4-8; PTX 963 at 27:20-28:23.)

253. When he first began working on the project, Dr. Kota consulted the patent and scientific literature regarding copolymer-1, including the patents-in-suit. (PTX 961 (Kota Dep.) at 31:7-14, 31:24-32:16, 40:15-42:22, 42:24-51:19; PTX 962 (B. Rao 06/09/2010 Dep.) at 26:8-27:4; PTX 963 (B. Rao 09/30/2010 Dep.) at 19:11-21:22.)

254. [redacted]

255. [redacted]

[redacted]

256. [redacted]

257. [redacted]

(b) ANDA Process

258. Section 3.2.S.2 of Mylan's ANDA, entitled "Manufacture," sets forth the manufacturing process for Mylan's proposed glatiramer acetate product. (PTX 321.) Although

Mylan has filed amendments to its ANDA, it has not revised its manufacturing process or produced any new exhibit batches since the original ANDA filing.

259. Mylan uses the same four-step process to make its glatiramer acetate active ingredient set forth in the patents-in-suit (the "patent process"), which is described above at paragraphs 196-203 above.

260. In Step 1 of the Mylan ANDA process, like in Step 1 of the patent process, the N-carboxyanhydrides of the amino acids alanine, glutamic acid, lysine, and tyrosine are combined with the initiator diethylamine to form long chains. (Sept. Tr. (Gokel) 348:13-22, 370:7-371:17; PTX 321 at MYL0000251, MYL0000260.)

261. As in the patent process, the glutamic acids and lysines used in Step 1 of the Mylan process must have benzyl and TFA protecting groups, respectively. (Sept. Tr. (Gokel) 342:16-343:23, 345:5-346:10; PTX 987 at 12-13.)

262. Step 1 results in a mixture of polypeptide chains that are referred to in Mylan's ANDA as GMA F1 or protected copolymer-1. (Sept. Tr. (Gokel) 371:18-21; PTX 321 at MYL0000251, MYL0000254; PTX 987 at 47-52.) Protected copolymer-1 still has the benzyl protecting groups on the glutamic acids and the TFA protecting groups on the lysines. (Sept. Tr. (Gokel) 371:18-372:18; PTX 321 at MYL0000251.)

263. In Step 2 of Mylan's process, as in the patent process, protected copolymer-1 is reacted with HBr/acetic acid. (Sept. Tr. (Gokel) 371:22-372:6; PTX 321 at MYL0000252; PTX 987 at 53-54.) Like in the patent process, the addition of HBr/acetic acid serves two purposes. First, it removes the benzyl protecting groups from the glutamic acids. Second, it cleaves, or cuts, the polypeptide chains. (Sept. Tr. (Gokel) 371:22-372:6; Sept. Tr. (Sampson) 1641:8-17; PTX 987 at 16-18.) The process of cleaving the polypeptide chains is known as

depolymerization. (Sept. Tr. (Gokel) 349:11-18; PTX 987 at 16-18, 53-54.)

264. The product of Mylan's Step 2 reaction is TFA-copolymer-1. (Sept. Tr. (Gokel) 371:22-372:18; PTX 987 at 53.)

265. As in the patent process, Step 2 is used to control the molecular weight of Mylan's product so that it meets the specification of 5,000 to 9,000 daltons. (Sept. Tr. (Gokel) 349:12-350:10, 371:22-372:6, 444:13-447:5; Sept. Tr. (Sampson) 1641:8-1642:8; PTX 321 at MYL0000645-651.)

266. In order to determine the time and temperature at which to run Step 2 so that the final copolymer-1 product has the targeted average molecular weight of between 5,000 and 9,000 daltons, Mylan ran a series of test reactions. (Sept. Tr. (Gokel) 445:4-447:11; PTX 321 at MYL0000645-49; PTX 961 (Kota Dep.) at 124:4-127:11.)

267. [redacted]

268. [redacted]

269. [redacted]

[redacted]

270. [redacted]

271. Mylan has applied the temperature and time determinations made based on the test reactions to its ANDA process. (Sept. Tr. (Gokel) 447:2-6; PTX 320 at MYL0000272-273; PTX 321 at MYL0000647, MYL0000649; PTX 964 at 120:23-122:9, 125:10-126:20.) [redacted]

272. This predetermined time and temperature for Step 2 allows Mylan to obtain copolymer-1 that meets its 5,000-9,000 daltons peak average molecular weight specification. (Sept. Tr. (Grant) 249:21-250:22, 251:8-20; PTX 300 at MYL0002928; PTX 312 at MYL0002930; PTX 313 at MYL0002932; PTX 318 at MYL0000107; PTX 321 at MYL0000651; PTX 325 at MYL0001050, 1068, 1079.)

273. [redacted]

[redacted]

274. In Step 3 of Mylan's process, TFA-copolymer-1 is treated with piperidine, which removes the TFA protecting groups from the lysines. (Sept. Tr. (Gokel) 372:14-18; PTX 321 at MYL0000253; PTX 987 at 55.) The patent process also employs this step.

275. In Step 4 of Mylan's process, as in the patent process, the resulting product from Step 3 is purified by diafiltration using acetic acid. (Sept. Tr. (Gokel) 372:14-23, 373:8-17; PTX 321 at MYL0000253, 267.)

276. The product of Step 4 is glatiramer acetate, or copolymer-1. (Sept. Tr. (Gokel) 372:14-18, 373:3-5; PTX 321 at MYL0000621; PTX 987 at 55.)

(3) Mylan's ANDA Product Label

277. The proposed label for Mylan's proposed product has the identical indication and dosage information as appears in Teva's label for Copaxone®. (Sept. Tr. (Lisak) at 141:13-

145:6; PTX 697; PTX 734 at MYL0004949.) Mylan's proposed product label states that the product is "indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis." (Sept. Tr. (Lisak) at 141:13-145:6; PTX 734 at MYL0004949.) If Mylan's product is approved by the FDA, its use would comprise a method of treating multiple sclerosis (Sept. Tr. (Lisak) at 145:21-146:1; 146:23-147:1), and Mylan's proposed label would encourage physicians to use the ANDA product to treat patients with multiple sclerosis. (Sept. Tr. (Lisak) 147:16-19; PTX 963 (B. Rao 09/30/2010 Dep.) at 226:17-22; PTX 971 (Talton Dep.) at 85:17-21.)

(ii) Sandoz ANDA Product

(1) Active Ingredient

278. The active ingredient in Sandoz's proposed product is described as glatiramer acetate. (Sept. Tr. (Gokel) 360:16-18.) As Sandoz and Momenta have acknowledged, glatiramer acetate is also known as copolymer-1. For example, Sandoz's labeling for its proposed product describes its active ingredient as "glatiramer acetate (formerly known as copolymer-1)." (Sept. Tr. (Lisak) 141:13-143:19; PTX 206 at SDZ00000031.) Sandoz internal documents likewise make clear that one of the names for its active ingredient is "copolymer-1." (Sept. Tr. (Grant) 220:13-221:7; PTX 141 at MMT00391607.) In addition, Momenta scientist Mani Iyer, who was in charge of manufacturing and developing Sandoz's glatiramer acetate, specifically testified that Sandoz's product is a "copolymer-1 composition." (PTX 960 (Iyer Dep.) at 25:8-10.)

(a) Amino Acid Composition

279. The glatiramer acetate active ingredient in Sandoz's proposed product is composed of the four amino acids glutamic acid, alanine, lysine and tyrosine. (Sept. Tr. (Gokel) 414:23-415:9; PTX 219 at SDZ00002024-25; PTX 351 at SDZ00018614.)

280. Sandoz's ANDA provides data on the relative proportions of glutamic acid,

alanine, lysine and tyrosine in its proposed product, expressed as molar fractions. (Sept. Tr. (Gokel) 417:19-22, 420:12-17; PTX 219 at SDZ00002025; PTX 913 at 28.) According to Sandoz's ANDA, the lots it produced have the following molar fractions of glutamic acid, alanine, tyrosine and lysine, respectively: drug substance lots 077K7277, 0.147: 0.436: 0.083: 0.334; drug substance lot 087K7253, 0.142: 0.419: 0.083: 0.356; drug product lot CT0743, 0.134: 0.444: 0.083: 0.340; and drug product lot CT0750, 0.126: 0.421: 0.083: 0.370. (Sept. Tr. (Gokel) 416:14-419:6; PTX 219 at SDZ00002025; PTX 987 at 89.)

281. [redacted] Sandoz provided the molar fractions for an additional drug substance lot, lot 051M7282. (Sept. Tr. (Gokel) 420:3-17.) The molar fractions of glutamic acid, alanine, tyrosine, and lysine for this lot are 0.136: 0.427: 0.093: 0.344. (Sept. Tr. (Gokel) 420:3-17; Sept. Tr. (Sampson) 546:22-547:15; PTX 913 at 28; PTX 987 at 93-95; PTX 988 at 3.) Sandoz has not formally amended its ANDA or manufacturing process to reflect this molar fraction.

(b) Molecular Weight

282. Sandoz's proposed product has a specification for peak average molecular weight between 5,000 and 9,000 daltons. (Sept. Tr. (Grant) 222:6-17.)

283. As set forth in Figure 8 below, the data in Sandoz's ANDA demonstrates that each of its lots falls within the specified 5,000-9,000 daltons range. (Sept. Tr. (Grant) 222:6-17; PTX 349 at SDZ00017949; PTX 351 at SDZ00018608-611; PTX 986 at 26.)

Figure 8

Lot	Peak Average Molecular Weight (Da)
077K7277	8407
087K7253	7275
058K7278	7216
078K7276	7104
128K7276	5932
029K7279	7641
049K7275	6977
049K7276	7366
059K7275	7199
CT0743	8274
CT0750	7417

Source: PTX 351 at SDZ00018608-11; PTX 349 at SDZ00017949

284. Sandoz determined these peak molecular weight values using SEC with TSK gel G 3,000 and G 2,000 columns. (Sept. Tr. (Grant) 214:19-215:5.) Sandoz calibrated the SEC columns using nine peptide standards that (i) had amino acid compositions consistent with the composition of copolymer-1 and (ii) had the same size-to-molecular weight relationship as copolymer-1. (Sept. Tr. (Grant) 215:6-13.)

285. In addition to having a specified peak molecular weight, Sandoz's product also has particular molecular weight distribution characteristics. (Sept. Tr. (Grant) 230:13-233:14; PTX 986 at 33.)

286. Dr. Grant used electronic molecular weight data generated by Sandoz during its SEC measurements of five Sandoz drug substance lots to calculate the percentage (on a molar fraction basis) of the copolymer-1 molecules in each lot that have a molecular weight between 2 and 20 kilodaltons and the percentage having molecular weights above 40 kilodaltons. (Sept. Tr. (Grant) 230:13-233:14.) These percentages are listed in Figure 9 below.

Figure 9

	% molar fraction between 2 and 20 kilodaltons (%)	% molar fraction above 40 kilodaltons (%)
077K7277	≥ 91.99	≤ 0.36
087K7253	≥ 85.00	≤ 0.28
049K7275	≥ 90.82	≤ 0.23
049K7276	≥ 87.36	≤ 0.24
059K7275	≥ 88.83	≤ 0.25

Source: PTX 377

287. Using the electronic molecular weight data for the same five Sandoz drug substance lots, Dr. Grant also calculated the molar fraction percentages of molecules having molecular weights between 2 and 20 kilodaltons in the TFA copolymer-1 intermediate that corresponded to each lot. (Sept. Tr. (Grant) 236:22-239:4; PTX 986 at 40.) These percentages are listed in Figure 10 below.

Figure 10

Trifluoroacetyl copolymer-1 corresponding to sample	% TFA molar fraction between 2 and 20 kilodaltons (%)
077K7277	≥ 91.45
087K7253	≥ 89.69
049K7275	≥ 92.82
049K7276	≥ 91.34
059K7275	≥ 92.07

Source: PTX 377

(2) Sandoz's Manufacturing Process

(a) Development of Process

288. Before it entered into the agreement with Momenta, Sandoz had worked on developing its own process for making generic Copaxone®. Dr. Anup Ray, a principal scientist

at Sandoz and its 30(b)(6) designee on Sandoz's processes for manufacturing copolymer-1, was tasked with this project. (PTX 364 (Topic 18); PTX 966 (Ray Dep.) at 18:13-15, 23:2-24:10, 30:13-16.)

289. The first thing Dr. Ray did after being given his assignment was to perform a literature search. (PTX 966 (Ray Dep.) at 32:13-15.) Following the literature search, Dr. Ray's initial strategy was to make generic Copaxone® using the method described in Teva's patent. (PTX 966 (Ray Dep.) at 42:6-15.)

290. Dr. Ray subsequently began work on developing alternative processes for making generic Copaxone®. (PTX 889; PTX 966 (Ray Dep.) at 81:11-83:20, 108:5-19.) Sandoz's strategy was to develop a route that "circumvented" Teva's patented method. (PTX 123 at SDZ00014130.) As Dr. Ray testified, he was receiving instructions from a Sandoz lawyer on these alternative processes. (PTX 966 (Ray Dep.) at 127:8-11.)

291. Dr. Ray eventually devised an alternative process for making copolymer-1 that he concluded was "very different from known Teva patented process." (PTX 115; *see also* PTX 117 at SDZ00011436; PTX 966 (Ray Dep.) at 92:6-11.) Sandoz filed a patent application on this process, and Dr. Ray was a named inventor. (PTX 155.)

292. Sandoz ultimately abandoned its attempts to circumvent Teva's patents and develop its own generic Copaxone® product and decided instead to collaborate with Momenta.

293. Momenta's efforts to design a process for making generic Copaxone® were led by Dr. Mani Iyer, who was then a Principal Scientist. (PTX 960 (Iyer Dep.) at 5:20-6:9, 16:20-21, 18:3-19:10, 19:20-20:2.)

294. Like Dr. Ray, the first thing Dr. Iyer did when given his assignment was to review the literature on copolymer-1, including the '808 patent. (Sept. Tr. (Bishop) 1075:19-1076:12;

PTX 960 (Iyer Dep.) at 19:23-20:2, 147:9-16.) Dr. Iyer understood that Teva's method for making copoymer-1 was a "Patented Process." (PTX 135; PTX 777; PTX 960 (Iyer Dep.) at 452:12-46:19.)

295. Momenta's process development strategy is set forth in a December 2005 presentation by Dr. Iyer. (PTX 141.) Phase I of the project was to replicate the "literature process." (PTX 141 at MMT00391608, 610-614.) The "literature process" was Momenta's internal designation for Teva's patented process. (PTX 960 (Iyer Dep.) at 130:7-9, 130:11-14, 130:17.) Phase II was to modify the process to "stay outside the process claims." (PTX 141 at MMT00391608, 647-51.) Phase III was to make further modifications to "add[] additional distance from a IP standpoint." (PTX 141 at MMT00391608, 652-56.)

296. Steve Brugger, Vice-President of Strategic Product Development for Momenta acknowledged in a presentation given to Sandoz that there were "[m]ultiple opportunities for development of alternate process." (PTX 119 at MMT01078913; PTX 957 (Brugger Dep.) at 74:19-75:10.)

297. Dr. Iyer's team worked on replicating the patented "literature process." (PTX 960 (Iyer Dep.) at 32:7-19, 32:21-22, 32:23-25.) At the same time, Momenta contracted out work on developing a "non-literature process." (PTX 960 (Iyer Dep.) at 32:7-19, 32:21-22, 32:23-25, 33:16-34:8.)

298. Momenta also did its own experimental work on an alternative non-literature process, and eventually filed a patent application on alternative routes for making copolymer-1. (PTX 177; PTX 785; PTX 960 (Iyer Dep.) at 159:24-160:18.)

299. Momenta stopped working on an alternative process in 2007, and decided to go forward with filing its ANDA using Teva's patented process. (PTX 960 (Iyer Dep.) at 37:7-10,

41:6-13, 113:16-19, 127:24-128:3, 130:7-17, 138:5-13; PTX 957 (Brugger Dep.) at 78:16-79:23.)

300. A May 2007 internal Momenta presentation explained Momenta's reasoning for abandoning the development of an alternative, non-infringing process. Momenta decided to file its ANDA using Teva's patented process because it "[e]nable[d] a first-to-file approach" and "[m]itigate[d] risk regarding chemical equivalence." (PTX 172 at MMT01287394.) In other words, as Dr. Iyer explained, Momenta decided to copy Teva's patented process for making copolymer-1 instead of developing its own process because it provided the quickest route to a regulatory filing. (PTX 960 (Iyer Dep.) at 127:18-128:3.) Dr. Iyer further testified that the time of 17 hours and a temperature of 26 degrees used in Step 2 of his process, the debenzylation step, was copied out of Teva's patent. (PTX 960 (Iyer Dep.) at 147:17-25, 148:3-7, 148:9-11.)

(b) ANDA Process

301. Sandoz's ANDA section 3.2.S.2.2, entitled "Description of Manufacturing Process and Process Controls (Glatiramer Acetate)," sets forth the details of Sandoz's manufacturing process for its proposed product. (Sept. Tr. (Gokel) 356:2-15; PTX 216 at SDZ00001937.) [redacted]

302. Broadly speaking, Sandoz uses the same four-step patent process to make its glatiramer acetate active ingredient that Mylan uses.

303. In Step 1, as in the patent process, Sandoz combines the N-carboxyanhydrides of alanine, benzyl protected glutamic acid, TFA protected lysine and tyrosine with the initiator diethylamine to form protected copolymer-1, which Sandoz calls Intermediate-1. (Sept. Tr. (Gokel) 348:13-22, 357:2-359:11; PTX 216 at SDZ00001937-38.)

304. In Step 2, as in the patent process, Intermediate-1 is reacted with HBr/acetic to form TFA protected copolymer-1, which Sandoz calls Intermediate-2. (Sept. Tr. (Gokel) 359:5-11, 368:4-8; PTX 216 at SDZ00001937-38.)

305. As in the patent process, the time and temperature of the Step 2 reaction is used to control the molecular weight of Sandoz's product and ensure that it meets the specification of 5,000 to 9,000 daltons. (Sept. Tr. (Gokel) 361:20-363:13; Sept. Tr. (Sampson) 1641:18-1642:8; PTX 213; PTX 214 at SDZ00000186.)

306. Sandoz determined the target time and temperature for Step 2 using "profile runs." (Sept. Tr. (Gokel) 424:12-425:15; PTX 214 at SDZ00000186.)

307. During these profile runs, samples of Intermediate-1 were taken at varying times during the Step 2 HBr/acetic acid reaction. (Sept. Tr. (Gokel) 424:12-425:15; PTX 214 at SDZ00000186.) The samples were then subjected to Steps 3 and 4 of Sandoz's manufacturing process and converted to glatiramer acetate. The average molecular weights of the resulting batches of glatiramer acetate were determined. (Sept. Tr. (Gokel) 424:12-425:15; PTX 214 at SDZ00000186.)

308. With this data, Sandoz was able to determine the window of time for the Step 2 reaction that would allow Sandoz to obtain a glatiramer acetate having an average molecular weight between 5,000 and 9,000 daltons. (Sept. Tr. (Gokel) 424:12-425:15; PTX 214 at SDZ00000186.)

309. The reaction conditions of time and temperature determined from the profile runs were applied to Sandoz's production batches. (Sept. Tr. (Gokel) 424:12-425:15; Sept. Tr. (Bishop) 1098:16-1099:6; PTX 214 at SDZ00000186.) [redacted]

[redacted]

310. In Step 3 of the Sandoz and patent processes, Intermediate-2 is treated with piperidine, which removes the TFA protecting groups from the lysines. (Sept. Tr. (Gokel) 359:17-360:9, 368:9-13; PTX 216 at SDZ00001937-38.) The resulting product is referred to in Sandoz's ANDA as Intermediate-3.

311. In Step 4, the final step of both the Sandoz and patent processes, Intermediate-3 is purified by a step called diafiltration. During this step, acetic acid is used. (Sept. Tr. (Gokel) 360:3-18, 361:3-19; PTX 216 at SDZ00001937-38, 949.) The product of Step 4 is glatiramer acetate, or copolymer-1. (Sept. Tr. (Gokel) 360:3-18; PTX 216 at SDZ00001937-38.)

(c) Briefing Book

312. [redacted]

313. The Briefing Book discusses using an in-process control based on viscosity to determine the endpoint of the Step 2 HBr/acetic acid reaction. (Sept. Tr. (Gokel) 426:3-427:6; PTX 913 at 36.) Viscosity is a property that describes the fluidity of a solution. (Sept. Tr. (Gokel) 427:7-11.) For example, gasoline or water have a low viscosity, whereas honey has a high viscosity. (Sept. Tr. (Gokel) 427:7-11.)

314. The Briefing Book does not provide details of the proposed viscosity in-process control method. The batch records for Sandoz's lots of glatiramer acetate, however, contain some additional information on the possible method. (PTX 928 at MMT01707032-040.)

315. According to the batch records there are actually two alternative methods for determining the endpoint of Step 2. (Sept. Tr. (Gokel) 430:7-25; PTX 914 at MMT01630951.)

316. The first alternative is the in-process control referred to in the Briefing Book, which Sandoz calls the "viscometer model." (Sept. Tr. (Gokel) 430:7-436:23; PTX 914 at MMT01630951-955; PTX 928 at MMT01707035.)

317. The premise of the viscometer model is that the viscosity of an Intermediate-1 sample at a given temperature can be correlated with the average molecular weight of the final glatiramer acetate product. (Sept. Tr. (Gokel) 426:3-427:6; PTX 913 at 36.) According to Sandoz's proposed method, the Step 2 HBr/acetic acid reaction would be stopped when a viscosity was reached that would provide a final glatiramer acetate product having the targeted average molecular weight of 7,300 daltons. (Sept. Tr. (Gokel) 432:11-23; PTX 914 at MMT01630953.)

318. The Intermediate-1 viscosity values that would give glatiramer acetate final product having the targeted average molecular weight of 7,300 daltons were previously determined by Sandoz using test reactions. In these test reactions, samples of Intermediate-1 were reacted with HBr/acetic acid at varying times and temperatures, and the viscosity values were measured. (Sept. Tr. (Gokel) 436:18-439:6; PTX 923 at MMT01694006, 106-114.) The samples of Intermediate-1 were then converted to glatiramer acetate, and the average molecular weights of the glatiramer acetate samples were determined. (Sept. Tr. (Gokel) 436:18-439:6; PTX 923 at MMT01694006, 106-114.)

319. Using this data, Sandoz determined what viscosity value of Intermediate-1 at a given temperature would result in final glatiramer acetate product having an average molecular weight of 7,300 daltons. (Sept. Tr. (Gokel) 436:18-439:6; PTX 923 at MMT01694006, 106-

114.)

320. Sandoz took the viscosity and temperature information it obtained and created a table of predetermined targeted viscosity values for given reaction temperatures. (Sept. Tr. (Gokel) 436:18-439:6; PTX 928 at MMT01707035.) The table contains temperatures ranging from 20.0°C to 24.0°C, in increments of two tenths of a degree, and their corresponding targeted viscosity values. (Sept. Tr. (Laird) 1159:19-1160:3; PTX 928 at MMT01707035.) The Step 2 reaction is stopped when the targeted viscosity value is reached for the Step 2 reaction temperature. (Sept. Tr. (Gokel) 430:17-431:24; PTX 914 at MMT01630952-953; PTX 928 at MMT01707035.)

321. Momenta documents indicate that as time increases, the viscosity decreases. (PTX 914 at MMT01630951-53.) Thus, the longer Intermediate-1 reacts with HBr/acetic acid, the lower its viscosity. This enables Sandoz to use viscosity, which changes as a function of time, rather than time itself to monitor the progress of the reaction and determine when to stop it in order to obtain a glatiramer acetate having an average molecular weight of 7,300 daltons. (Sept. Tr. (Gokel) 430:7-16, 434:9-17.)

322. The second alternative method for determining the endpoint of the Step 2 reaction described in Sandoz's batch records is a "time and temperature model." It is to be used "[i]n the event of the viscometer equipment failure or the inability to obtain accurate viscosity readings . . . ." (Sept. Tr. (Laird) 1160:20-25; PTX 928 at MMT01707035-036.) Like the viscometer model, the "time and temperature model" utilizes a table with temperatures ranging from 20.0°C to 24.0°C, but time, rather than viscosity, at a given temperature is used to determine when to stop the HBr/acetic acid reaction in order to achieve a final glatiramer acetate product having an average molecular weight of 7,300 daltons. (PTX 928 at MMT01707036.)

323. The time and temperature values in the table are based on results of prior test reactions. (Sept. Tr. (Gokel) 436:18-439:6; PTX 923 at MMT01694006, 115-124.) In these test reactions, samples of Intermediate-1 were reacted with HBr/acetic acid at varying times and temperatures. (Sept. Tr. (Gokel) 436:18-439:6; PTX 923 at MMT01694006, 115-124.) The samples of Intermediate-1 were then converted into glatiramer acetate, and the average molecular weight of the samples of glatiramer acetate were determined. (Sept. Tr. (Gokel) 436:18-439:6; PTX 923 at MMT01694006, 115-124.)

324. Using this data, Sandoz determined how time and temperature correlated with a final glatiramer acetate product having an average molecular weight of 7300 daltons. (Sept. Tr. (Gokel) 436:18-439:6; PTX 923 at MMT01694006, 115-124.) This information was used to create the time and temperature table. (Sept. Tr. (Gokel) 436:18-439:6; PTX 923 at MMT01694006, 115-124.)

325. As explained above, the current batch records set forth both a viscometer model and a time and temperature model. (Sept. Tr. (Laird) 1158:17-18, 1163:2-4; PTX 928 at MMT01707035-036.) If Sandoz submits to the FDA any future amendments to its ANDA, it must submit the underlying batch records. (Sept. Tr. (Laird) 1157:11-14.) Thus, the FDA would receive batch records containing both the viscometer model and the time and temperature model.

(3) Sandoz's ANDA Product Label

326. The proposed label for Sandoz's ANDA product has the identical indication and dosage information as in Teva's Copaxone® label. (Sept. Tr. (Lisak) 141:13-145:6; PTX 206 at SDZ00000034, 044; PTX 697.) Sandoz's proposed product label states that the product is "indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis." (Sept. Tr. (Lisak) 141:13-145:6; PTX 206 at SDZ00000034.) If Sandoz's ANDA product was approved by the FDA, its use would comprise a method of treating multiple

sclerosis (Sept. Tr. (Lisak) at 145:21-146:1, 146:23-147:1), and Sandoz's proposed label would encourage physicians to use the ANDA product to treat patients with multiple sclerosis. (Sept. Tr. (Lisak) 147:16-19.)

C. Conclusions of Law

(i) Mylan's Proposed Product Infringes Each of the Asserted Claims

327. Plaintiffs presented evidence at trial that Mylan's proposed product meets each and every limitation of the asserted claims. (Sept. Tr. (Gokel) 399:5-9, 400:12-20, 448:16-469:7; PTX 987 at 101-110.) With the exception of the claim term "copolymer-1," Mylan submitted no evidence contesting infringement of any of the claim limitations. For the reasons set forth below, Mylan's proposed product infringes each of the asserted claims.

(1) Mylan's Product is Copolymer-1

328. Mylan represented to the FDA in numerous places in its ANDA that the active ingredient in its proposed product is "copolymer-1." (Sept. Tr. (Grant) 250:7-9; Sept. Tr. (Owens) 629:1-12, 630:11-631:8; Sept. Tr. (Gokel) 369:21-370:3, 372:14-18; PTX 320 at MYL0000236, 253; PTX 734 at MYL0004956; PTX 962 (B. Rao 06/09/2010 Dep.) at 192:6-10; PTX 987 at 55.) Notwithstanding what it told the FDA outside the context of this litigation, Mylan now argues that its product is not copolymer-1. The evidence at trial was to the contrary.

329. The claim term "copolymer-1" has been construed to mean "a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6:2:5:1, respectively, non-uniform with respect to molecular weight and sequence, which is synthesized by polymerization of suitably protected amino acid carboxyanhydrides." (Claim Construction Order at 12.)

330. Mylan does not contest that its product is a "mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine;" that it is "non-uniform with respect to molecular

weight and sequence;" and is "synthesized by polymerization of suitably protected amino acid carboxyanhydrides;" and the evidence at trial established that Mylan's proposed product does in fact meet those limitations. (Sept. Tr. (Grant) 250:7-12; Sept. Tr. (Gokel) 377:5-378:10; 413:22-415:9.)

331. Mylan argues, however, that its product is not copolymer-1 because the amino acids in its product are not "in a molar ratio of approximately 6:2:5:1." As the evidence showed, however, Mylan's product does have a molar ratio of approximately 6:2:5:1 and is therefore copolymer-1 within the meaning of the claims.

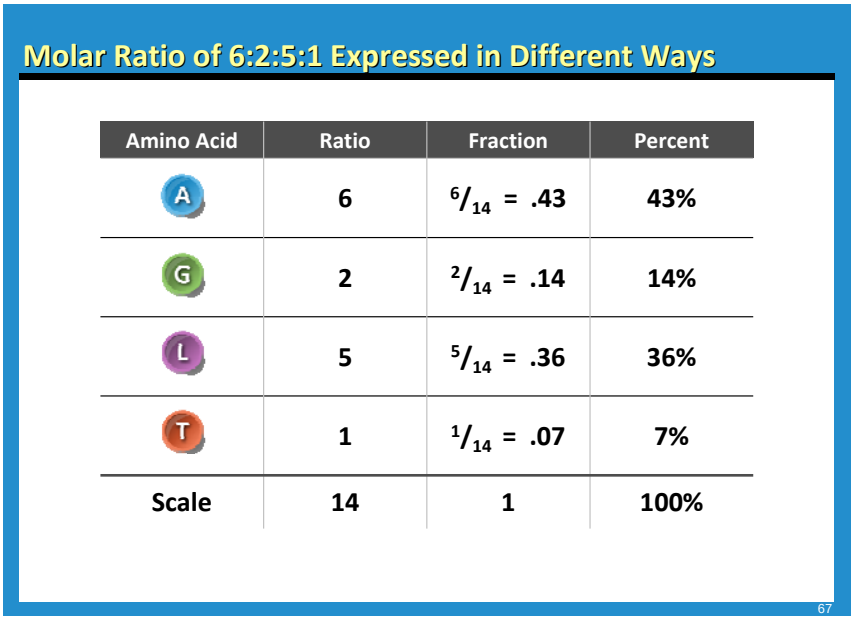
332. A "molar ratio" is a means of expressing the relative proportions of each of the components in a mixture. (Sept. Tr. (Gokel) 378:20-379:11.)

333. The molar ratio of "approximately 6:2:5:1" describes the relative proportions of the four amino acids alanine, glutamic acid, lysine and tyrosine in copolymer-1. (Sept. Tr. (Gokel) 411:21-412:1.) For every 14 amino acids, approximately 6 will be alanine, approximately 2 will be glutamic acid, approximately 5 will be lysine, and approximately 1 will be tyrosine. (Sept. Tr. (Gokel) 381:6-14; PTX 987 at 67.)

334. Because the sum of 6 + 2 +5 +1 is 14, the molar ratio 6:2:5:1 is expressed on a scale of 14. (Sept. Tr. (Gokel) 411:24-412:1.)

335. As can be seen in Figure 11 below, the molar ratio of 6:2:5:1 can be expressed in different ways.

Figure 11



(PTX 987 at 67.)

336. For example, approximately 6:2:5:1 can be expressed as the percentages of the four amino acids in a copolymer-1 mixture, which by definition must add up to 100%: approximately 6 out of 14, or approximately 43%, are alanine; approximately 2 out of 14, or approximately 14%, are glutamic acid; approximately 5 out of 14, or approximately 36%, are lysine; and approximately 1 out of 14, or approximately 7%, are tyrosine. (Sept. Tr. (Gokel) 381:24-382:3; PTX 987 at 67.)

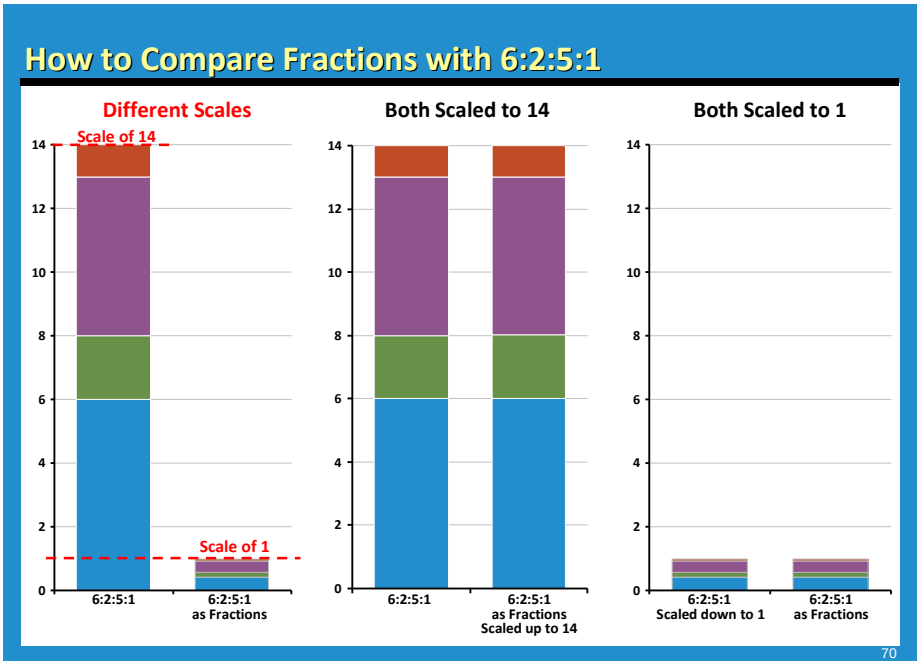
337. The molar ratio of approximately 6:2:5:1 can also be expressed in terms of molar fractions, which by definition must add up to 1. In that case, the molar fraction of alanine would be approximately 0.43; the molar fraction of glutamic acid would be approximately 0.14; the molar fraction of lysine would be approximately 0.36 and the molar fraction of tyrosine would be approximately 0.07. (Sept. Tr. (Gokel) 381:6-14; PTX 987 at 67.)

338. Whether expressed as (1) "approximately 6:2:5:1;" (2) approximately 43% alanine, 14% glutamic acid, 36% lysine, and 7% tyrosine; or (3) approximate molar fractions of

0.43 alanine:0.14 glutamic acid:0.36 lysine: 0.07 tyrosine, the molar fractions all represent the same copolymer-1 compositions with the same relative proportions of the same four amino acids. (Sept. Tr. (Gokel) 381:6-382:15; PTX 987 at 67.)

339. In order to determine whether a sample has a molar ratio of "approximately 6:2:5:1," one can compare the sample using the 6:2:5:1 scale of 14; the percentages of the amino acids scale of 100%, or the molar fraction scale of 1. What is critical, however, is that the amino acid composition of the sample and 6:2:5:1 be expressed on the same scale. (Sept. Tr. (Gokel) 382:23-383:15.). If the two are compared on different scales, it will give skewed results as demonstrated in Figure 12 below.

Figure 12



(PTX 987 at 70.)

340. In its ANDA, Mylan provides the molar ratios for its proposed product in terms of molar fraction. (Sept. Tr. (Owens 629:19-21; Sept. Tr. (Gokel) 394:17-396:21, 399:20-400:1, 400:4-6; Sept. Tr. (Owens) 629:19-21; PTX 300 at MYL0002927; PTX 312 at MYL0002929;

PTX 313 at MYL0002931; PTX 325 at MYL0001050; PTX 961 (Kota Dep.) at 111:25-112:16; PTX 987 at 74, 77, 78.) In order to determine whether Mylan's product meets the "approximately 6:2:5:1" limitation, "6:2:5:1" can be converted to molar fractions and then compared directly to the molar fractions in Mylan's ANDA. Alternatively, Mylan's molar fraction data can be converted to a scale of 14 and then compared directly to 6:2:5:1. (Sept. Tr. (Gokel) 395:17-387:25; PTX 987 at 74-75.) The data for Mylan's Drug Substance Lot GMA/001/009 are compared both ways in Figure 13 below:

Figure 13

Mylan Drug Substance Lot GMA/001/09

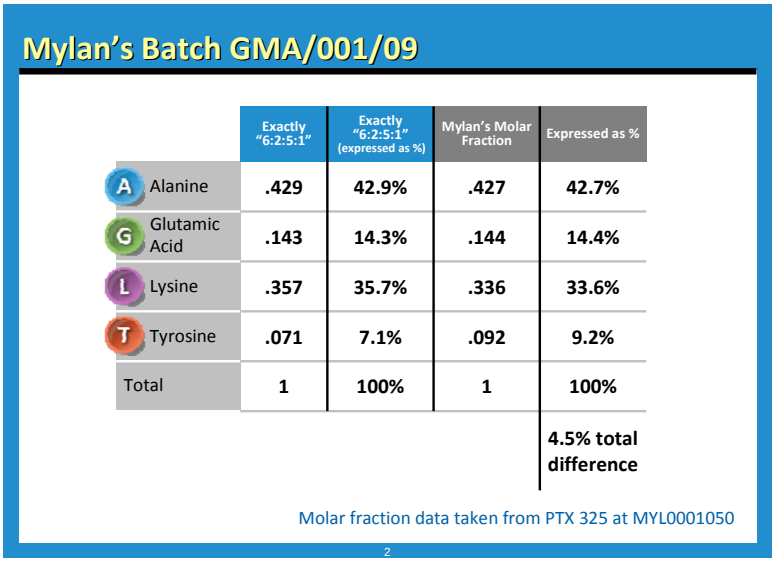
Amino Acid	6:2:5:1	6:2:5:1 (Scale = 1)	Lot GMA/001/09 (Scale = 1)		Scale = 14	
A	6	.43	.427	x 14	5.98	6
G	2	.14	.144	x 14	2.02	2
L	5	.36	.336	x 14	4.70	5
T	1	.07	.092	x 14	1.29	1
Scale	14	1	1		14	14

74

(Sept. Tr. (Gokel) 396:3-397:9; PTX 987 at 74.)

341. Mylan's molar fraction data and 6:2:5:1 could also be converted to percentages and then compared directly. That comparison is shown in Figure 14 below:

Figure 14



(Sept. Tr. (Sampson) 543:1-544:17; PTX 988 at 2.)

342. As is shown, copolymer-1 with a molar ratio of exactly 6:2:5:1 would have 42.9% alanine, 14.3% glutamic acid, 35.7% lysine, and 7.1% tyrosine. Using the molar fractions reported for GMA/001/09 in Mylan's ANDA, the percentages of each amino acid in the batch are 42.7% alanine, 14.4% glutamic acid, 33.6% lysine, and 9.2% tyrosine. (PTX 988 at 2; Sept. Trial (Sampson) 543:22-545:4; PTX 988 at 2.) The percent differences in alanine, glutamic acid, lysine and tyrosine are therefore 0.2, 0.1, 2.1, and 2.1 percentage points, respectively, resulting in a percent total difference of 4.5% between the molar ratio of Mylan's product and exactly 6:2:5:1. (Sept. Trial (Sampson) 543:14-545:4; PTX 988 at 2.)

343. Mylan's expert Dr. Kent testified that that the difference in the molar fraction of tyrosine between Mylan's product and a product with a molar ratio of exactly 6:2:5:1 is 30%. This is incorrect. As Dr. Sampson testified, although as a matter of arithmetic there is a 30% difference between the numbers .071 (molar fraction of tyrosine in a product of *exactly* 6:2:5:1) and .092 (molar fraction of tyrosine in Mylan's product), that does *not* mean that the molar ratios

differ by 30%. Dr. Sampson explained that in order to properly compare the molar fractions, one has to look at the compositions of the two copolymers in their entirety and not simply focus on a single amino acid. Looking at the compositions as a whole, there is a 2.1% difference in the tyrosine content, since one batch has 7.1% and the other has 9.2%. (Sept. Tr. (Sampson) 545:23-546:20.)

344. In order to determine whether this 4.5% total difference in amino acid content falls within the scope of "approximately," the Court is guided by the specification of the patents-in-suit and their prosecution history. *See Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1056 (Fed. Cir. 1988) ("We note that the height and position limitation in the claim are modified by the terms 'substantially' and 'approximately.' These terms must be interpreted in light of the specification and prosecution history to determine the literal coverage of the claims with respect to height and position.").

345. Turning first to the specification, the person of ordinary skill in the art would understand that the molar ratio of 6:2:5:1 is reported in one significant figure. In other words, it is reported as 6:2:5:1 rather than, for example, 6.0: 2.0: 5.0: 1.0. This would indicate to the person of ordinary skill that each of those whole numbers, 6, 2, 5, and 1 is not precise, but encompasses the rounding range associated with it. (Sept. Tr. (Gokel) 384:4-385:8.)

346. The person of ordinary skill in the art would also understand that the specification of the patents-in-suit cites to Teitelbaum 1971 in connection with the description of copolymer-1. Thus, one of ordinary skill would look to that article in order to gain an understanding of the scope of "approximately 6:2:5:1." (PTX 1 at col. 1, ll. 23-29; Sept. Tr. (Gokel) 387:25-389:8; PTX 499.)

347. Table 1 of Teitelbaum 1971 is entitled "Composition of copolymer 1." It

provides, among other things, the molar ratios for two batches that are expressly defined as "copolymer-1." Copolymer-1 Batch 1 is reported as having a molar ratio for alanine, glutamic acid, lysine, and tyrosine of 6.0: 1.9: 4.7: 1.0. Copolymer-1 Batch 2 is reported as having a molar ratio for alanine, glutamic acid, lysine, and tyrosine of 6.7: 2.1: 4.2: 1.0. (Sept. Tr. (Gokel) 390:16-25; Sept. Tr. (Sampson) 550:18-551:2; PTX 499 at 243; Sept. Tr. (Kent) 726:16-24.)

348. The authors report in the article that they considered the amino acid compositions of the two batches to be the same. (PTX 499 at 247; Sept. Tr. (Sampson) 552:12-18.)

349. The total percent difference between the molar ratio of Teitelbaum 1971 Batch 2 and the molar ratio of exactly 6:2:5:1 is 12%. One of ordinary skill in the art would understand that the scope of "approximately 6:2:5:1" must be broad enough to include the molar ratio of Teitelbaum 1971 batch 2, which was expressly defined as copolymer-1. Thus, the scope of "approximately 6:2:5:1" must, at a minimum, include total amino acid content differences of up to 12% from exactly 6:2:5:1. (Sept. Tr. (Gokel) 391:1-392:15; Sept. Tr. (Sampson) 551:3-21; PTX 987 at 71; PTX 499 at 243; PTX 988 at 5.)

350. The prosecution history of the '539 patent in suit also provides guidance on the scope of "approximately 6:2:5:1." In a December 1, 2004 submission to the PTO during prosecution of the '539 patent, Teva amended the claims to recite "copolymer-1" and explained to the PTO the meaning of that term as used in the claims. (PTX 20-A at TEV000304802.)

351. As Teva told the PTO, "the term 'copolymer-1' is not limited to a specific molar ratio of amino acids." Teva explained that "[t]he molar ratio of the polypeptides of 'copolymer-1' varies slightly based on the particular batch and the particular analytical methodology used." As an example, Teva pointed to the two batches of copolymer-1 in Teitelbaum 1971 discussed

above. (PTX 20-A at TEV000304802; Sept. Tr. (Kent) 736:17-737:10; PTX 20-A at TEV000304802.)

352. Teva also pointed to three batches of copolymer-1 used in the Bornstein trial that had molar ratios of "1.9: 4.0: 6.0: 1.0," "1.8: 3.9: 5.7: 1.0," and "1.9: 4.0: 6.3: 1.0." (PTX 20-A at TEV000304802; Sept. Trial. Tr. (Kent) 737:11-22.) These molar rations rearranged and expressed as ratios of alanine to glutamic acid to lysine to tyrosine are 6.0: 1.9: 4.0: 1.0, 5.7: 1.8: 3.9: 1.0, and 6.3: 4.0: 1.9: 1.0.

353. Based on the prosecution history, the term "approximately 6:2:5:1" must be broad enough to include the molar ratios of the Teitelbaum 1971 batches as well as those of the three Bornstein batches, all of which were expressly defined as copolymer-1. *See Monsanto Co. v. Bayer Bioscience N.V.*, 363 F.3d 1235, 1244-45 (Fed. Cir. 2004) (district court improperly limited claims to a particular class of plants where the specification and prosecution history contained express statements that applicants had not limited claims in such a manner).

354. Since the amino acid molar ratio of Mylan's proposed product differs from exactly "6:2:5:1" by only 4.5%, it is closer to exactly 6:2:5:1 than are the amino acid molar ratios of either Teitelbaum Batch 2 or the Bornstein batches referred to in the prosecution history. Therefore, Mylan's product must fall within the scope of "approximately 6:2:5:1."

355. Mylan's argument for why its product does not meet the "approximately 6:2:5:1" limitation, and is therefore not copolymer-1, rests on the testimony of its expert Dr. Kent. In Dr. Kent's opinion, in order to determine whether Mylan's copolymer-1 meets the "approximately 6:2:5:1" requirement, the molar fractions for each of the four amino acids provided in Mylan's ANDA must first be divided by the molar fraction for tyrosine. (Sept. Tr. (Kent) 701:6-23.) This mathematical procedure is referred to as normalizing to tyrosine. (Sept. Tr. (Gokel) 400:21-

401:20.) The resulting values for glutamic acid, lysine, alanine and tyrosine must then be compared directly to 6, 2, 5, and 1, respectively. (Sept. Tr. (Kent) 701:6-702:13.) According to Dr. Kent, if the value of any single amino acid differs by more than 10%, the composition cannot be copolymer-1. (Sept. Tr. (Kent) 703:5-704:8.)

356. Dr. Kent's opinion about the meaning and scope of approximately 6:2:5:1 in this case cannot be correct for several reasons.

357. First, Dr. Kent's opinion on the scope of "approximately 6:2:5:1" cannot be correct because it would exclude from the definition of copolymer-1 batches that the inventors themselves identified as copolymer-1 and batches that Teva expressly represented to the PTO were copolymer-1. *See Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 909 (Fed. Cir. 2004) (district court erred in construing claim term narrowly where prosecution history showed that patentee intended a broader scope).

358. As Dr. Kent testified at trial, using his definition of "approximately 6:2:5:1," Teitelbaum 1971 Batch 2 is not copolymer-1 despite the fact that the inventors themselves defined it as copolymer-1. (Sept. Tr. (Kent) 726:16-24, 728:18-24.) While Dr. Kent attempted to explain away this flaw in his opinion by asserting that the molar ratio of Batch 2 never appeared in the literature after Teitelbaum 1971, he eventually conceded that it was reported in at least two later publications. (Sept. Tr. (Kent) 731:4-22; PTX 508 at 280; Sept. Tr. (Kent) 732:6-733:4; PTX 976 at 285.)

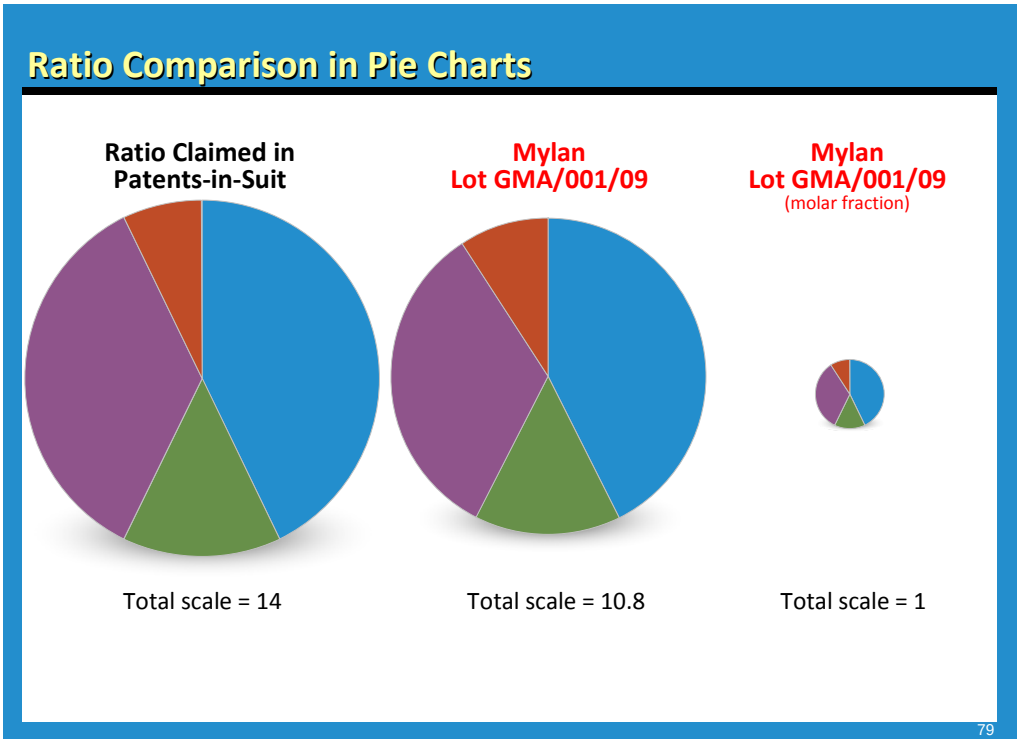
359. Dr. Kent similarly testified that the three Bornstein batches that Teva expressly identified as copolymer-1 during prosecution of the '539 patent were also not copolymer-1 using his definition of "approximately 6:2:5:1." (Sept. Tr. (Kent) 741:3-18.)

360. Second, there is simply no requirement that Mylan's molar fraction data be normalized to tyrosine before comparing it to 6:2:5:1 as Dr. Kent suggests. The patents-in-suit make no mention of normalizing to tyrosine. (Sept. Tr. (Kent) 749:3-6.) And despite testifying that it is common practice to normalize to the least abundant species, Dr. Kent conceded that he does not do so in his own work outside the context of this litigation. (Sept. Tr. (Kent) 747:22-748:16.)

361. Significantly, Dr. Kent admitted during cross-examination that the best way to compare the amino acid compositions of samples is by comparing their molar fractions, *not* their molar ratios. (Sept. Tr. (Kent) 743:10-15; 744:1-13.) As Dr. Kent also acknowledged, you could use either molar ratios or molar fractions to determine whether a sample had a molar ratio of approximately 6:2:5:1. (Sept. Tr. (Kent) 743:16-21.)

362. Moreover, as discussed above, the molar ratio of Mylan's product cannot be directly compared to 6:2:5:1 unless both numbers are on the same scale. (Sept. Tr. (Gokel) 382:23-383:15, 401:21-402:9; PTX 987 at 68.) As set forth above, "approximately 6:2:5:1" is expressed on a scale of 14. Mylan's molar ratio data in its ANDA is expressed as molar fractions on a scale of 1. Normalizing this molar fraction data to tyrosine as Dr. Kent requires converts Mylan's molar ratio to a scale of 10.8. As shown in Figure 15 below, this puts the numbers on different scales and leads to an invalid comparison. (Sept. Tr. (Gokel) 400:21-402:9, 411:14-412:19; Sept. Tr. (Sampson) 555:24-556:11; (PTX 987 at 79.)

Figure 15



363. Finally, Dr. Kent testified that a copolymer-1 molar ratio of approximately 6:2:5:1 *requires* the presence of a bromotyrosine impurity. (Sept. Tr. (Kent) 756:9-757:18.) Following this view to its logical conclusion. pure copolymer-1 with no impurities would not fall within the Court's construction of copolymer-1. Indeed, Dr. Kent testified that if a person of ordinary skill in the art followed the exact procedure for making copolymer-1 described in the patents-in-suit and used high quality HBr with no free bromine in it, the resulting product would not be copolymer-1. (Sept. Tr. (Kent) 758:10-24.) This cannot be the case.

364. For the reasons discussed above, Mylan's proposed product falls within the literal scope of "approximately 6:2:5:1" and is therefore copolymer-1 within the meaning of the claims.

(a) The molar ratio of Mylan's product is insubstantially different from "approximately 6:2:5:1"

365. Even if Mylan's product did not literally meet the requirement of a molar ratio of "approximately 6:2:5:1," it would meet that requirement under the doctrine of equivalents. *See Boehringer Ingelheim Vetmedica*, 320 F.3d at 1351 ("Under the doctrine of equivalents, a claim limitation not literally met may be satisfied by an element of the accused product if the differences between the two are "insubstantial" to one of ordinary skill in the art").

366. Dr. Sampson testified at trial that the difference between the molar ratio of Mylan's proposed product and "approximately 6:2:5:1" is insubstantial and that it is therefore equivalent to "approximately 6:2:5:1." (Sept. Tr. (Sampson) 543:14-545:4, 552:24-553:15; 557:20-23.) Her testimony was unrebutted.

367. In support of her opinion, Dr. Sampson pointed to, among other things, the data in Teitelbaum 1971.

368. As set forth above, Table 1 of Teitelbaum 1971 shows the molar ratios for two batches of copolymer-1. The molar ratio of alanine, glutamic acid, lysine, and tyrosine for batch 1 is 6.0: 1.9: 4.7: 1.0 and the molar ratio for batch 2 is 6.7: 2.1: 4.2: 1.0. (PTX 499; Sept. Tr. (Sampson) 550:18-551:2.)

369. As Dr. Sampson testified, there is a 2% total difference between the molar ratio of batch 1 and exactly 6:2:5:1 and a 12% total difference between the molar ratio of batch 2 and exactly 6:2:5:1. (PTX 988 at 5; Sept. Tr. (Sampson) 552:3-21.) Despite these differences in molar ratio, the two batches were reported as being equally effective in suppressing experimental allergic encephalomyelitis (EAE), an animal model for multiple sclerosis, in guinea pigs. (Sept. Tr. (Sampson) 549:11-24; PTX 499 at 247 (Table 8)) In fact, the authors themselves concluded that the two batches of copolymer-1 showed similar biological activity. (PTX 499 at 247; Sept.

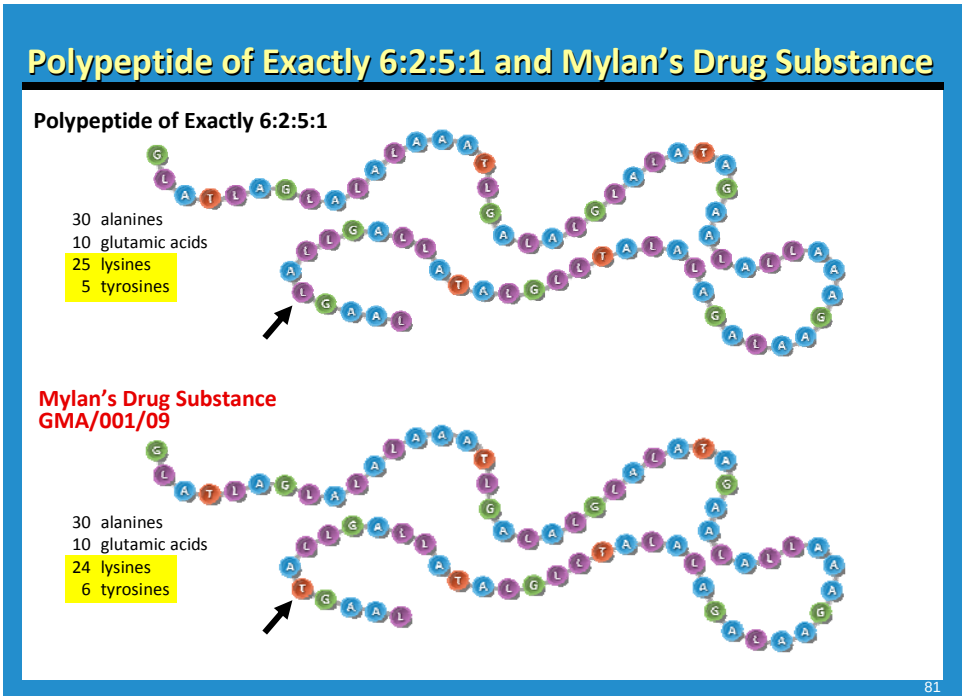
Tr. (Sampson) 552:12-18.)

370. Thus, as Dr. Sampson testified, Teitelbaum 1971 demonstrates that a total amino acid difference of up to 12% from exactly 6:2:5:1 does not materially affect the biological activity of a copolymer-1 sample. Mylan's Drug Substance, which differs from exactly "6:2:5:1" by only 4.5%, would therefore not be expected to have materially different biological activity from a copolymer-1 sample with a molar ratio of exactly 6:2:5:1. (Sept. Tr. (Sampson) 552:14-553:15.) Indeed, Mylan's own testing of its product demonstrates that it is active in the EAE model as are both Teitelbaum 1971 batches. (PTX 318; Sept. Tr. (Owens) 640:23-641:17.)

371. Accordingly, the molar ratio of Mylan's proposed product is insubstantially different from "approximately "6:2:5:1." (Sept. Tr. (Sampson) 543:14-544:17, 552:14-553:15.) *See Boehringer Ingelheim Vetmedica*, 320 F.3d at 1351 (relying on similar biological properties to conclude that claimed and accused elements were insubstantially different and, therefore, equivalent).)

372. Dr. Sampson also explained that the 4.5% total difference between the molar ratio of the amino acids in Mylan's proposed product and exactly 6:2:5:1 translates into a single amino acid difference for an average copolymer-1 chain with 70 amino acids, which would have a molecular weight of about 7,500 daltons. (Sept. Tr. (Sampson) 548:1-18.) This single amino acid difference is illustrated in Figure 16 below.

Figure 16



(PTX 987 at 81; *see also* PTX 988 at 4.)

373. By contrast, as can be seen in Figure 17 below, there is a four amino acid difference in that same 70 amino acid chain between batch 2 of Teitelbaum 1971 and a polypeptide having a molar ratio of exactly "6:2:5:1." (Sept. Tr. (Sampson) 556:12-557:19.)

Figure 17

(PTX 988 at 10.)

374. This single amino acid difference in Mylan's product cannot be viewed as substantial in light of the four amino acid differences ofTeitelbaum Batch 2, which is expressly defined as copolymer-1.

375. For these reasons, even if the molar ratio of the amino acids in Mylan's product did not fall within the literal scope of "approximately 6:2:5:1" (which, as set forth above, it does) it would be equivalent to "approximately 6:2:5:1."

(2) Mylan's Product Meets the Molecular Weight Limitations

376. The molecular weight limitations of the asserted claims can be divided into three categories: average molecular weight limitations; copolymer-1 fraction limitations; and TFA copolymer-1 fraction limitations.

377. Dr. Grant explained at trial why Mylan's ANDA product meets the molecular weight limitations of each of the asserted claims. (Sept. Tr. (Grant) 265:2-268:3.) Mylan did not offer any testimony to rebut Dr. Grant's conclusions.

(a) Average molecular weight limitations

378. "Average molecular weight" has been construed to mean "peak molecular weight detected using an appropriately calibrated suitable gel filtration column." (Claim Construction Order at 40 and n.10; Sept. Tr. (Grant) 211:5-15; PTX 986 at 25.)

379. As Dr. Grant testified, Mylan's method for determining the peak molecular weight values of its product involves using an appropriately calibrated suitable gel filtration column. (Sept. Tr. (Grant) 250:23-254:22; PTX 318 at MYL0000111-12; PTX 330 at MYL0000765-766.)

380. Based on Dr. Grant's testimony and the peak molecular weight data in Mylan's ANDA, Mylan's proposed product meets the molecular weight limitations of claims 1 of the '808 patent and claim 1 of the '589 patent, which require a copolymer-1 having an average molecular weight of "about 5 to 9 kilodaltons;" claims 1 and 6 of the '847 patent and claims 1, 8, 9, 12, 23, 30, and 31 of the '539 patent, which require a copolymer-1 having an average molecular weight of "about 4 to about 9 kilodaltons;" and claim 10 of the '539 patent, which requires a copolymer-1 with an average molecular weight of "6.25 to 8.4 kilodaltons." (Sept. Tr. (Grant) 259:24-260:22; PTX 986 at 24, 45.)

(b) Copolymer-1 molar fraction limitations

381. Based on Dr. Grant's calculations using Mylan's electronic data, Mylan's proposed product meets the molecular weight limitations of Claims 1-3 of the '430 patent, which require the copolymer-1 to have over 75% of its molar fraction within the molecular weight range of 2 and 20 kDa; claims 8 and 30 of the '539 patent, which require the copolymer-1 to have less than 2.5% of its molar fraction with molecular weights above 40 kDa; claims 9, 10, and 31 of the '539 patent and claim 8 of the '098 patent, which require that the copolymer-1 have over 75% of its molar fraction between the molecular weights of 2 and 20 kDa and less than

2.5% of its molar fraction with molecular weights greater than 40 kDa; claim 1 of the '476 patent, claim 1 of the '161 patent, and claim 1 of the '098 patent which require that the copolymer-1 have over 75% of its molar fraction between the molecular weights of 2 and 20 kDa and less than 5% of its molar fraction with molecular weights greater than 40 kDa. (Sept. Tr. (Grant) 262:14-263:21; 463:16-1465:25; 1466:9-19.)

(c) TFA copolymer-1 molar fraction limitations

382. Based on Dr. Grant's calculations using Mylan's electronic data, Mylan's proposed product meets the molecular weight limitations of Claims 1-3 of the '430 patent, claim 1 of the '476 patent, and claim 1 of the '161 patent, which require that the TFA copolymer-1 that is made as a result of treatment of protected copolymer-1 with hydrobromic acid have over 75% of its molar fraction with molecular weights between 2 and 20 kDa. (Sept. Tr. (Grant) 265:2-15.)

(3) Mylan's Process Meets the Process Limitations

383. Of the 22 asserted claims of the patents-in-suit, twelve claims are directed either to a method of manufacturing copolymer-1 or to a copolymer-1 that is made by a particular process. Mylan has not disputed that the manufacturing process in its ANDA meets these claim limitations.

384. [redacted]

[redacted]

(4) Mylan Meets the Treatment Limitations

385. Dr. Lisak testified at trial regarding Mylan's infringement of the claim limitations related to treatment of multiple sclerosis. Dr. Lisak's testimony was unrebuttted.

386. Based on Dr. Lisak's testimony, Mylan's proposed product meets the "method of treating multiple sclerosis" limitation found in claim 1 of the '476 patent; the "administering to a subject in need thereof" limitation found in claim 1 of the '476 patent; the "pharmaceutically effective amount" limitation found in claim 1 of the '476 patent and claim 1 of the '161 patent; the "treatment of multiple sclerosis" limitation found in claim 1 of the '161 patent; the "suitable for treating multiple sclerosis" limitation found in claim 1 of the '539 patent; the "dose therapeutically effective to treat multiple sclerosis" found in claim 12 of the '539 patent; the "a method for treating a patient suffering from multiple sclerosis" found in claims 23, 30, and 31 of the '539 patent; the "administering to a patient in need thereof" limitation found in claims 23, 30, and 31 of the '539 patent; and the "suitable for treating multiple sclerosis" limitation found in claim 1 of the '098 patent. (Sept. Tr. (Lisak) 137:5-147:19; PTX 734 at MYL0004949; PTX 985 at 20.)

387. In addition, based on the stipulation entered into by mylan, Mylan's proposed product meets the limitations of "pharmaceutical composition" and "pharmaceutically acceptable

excipient" in claims 12, 23, 30, and 31 of the '539 patent. (PTX 935.)

388. Finally, Mylan will induce physicians to infringe the '476 and '539 patents should its ANDA be approved. Mylan knew of those patents before filing its ANDA, as it filed a certification with the FDA and sent a notice letter to Teva specifically referencing the patents-in-suit, including the '476 and'539 patents. (*See* PTX 965 (S. Rao Dep.) at 123:25-124:14; Pretrial Order at ¶¶ 89-90, 94-95.) Mylan's proposed product label will induce doctors to prescribe its ANDA product for treatment of multiple sclerosis and thereby induce infringement of claim 1 of the '476 patent and claims 23, 30, and 31 of the '539 patent. *See AstraZeneca LP*, 633 F.3d at 1060-61 ("The pertinent question is whether the proposed label instructs users to perform the patented method. If so, the proposed label may provide evidence of [the alleged infringer's] affirmative intent to induce infringement."); *see also Wyeth*, 703 F. Supp. 2d 508, 521 (E.D.N.C 2010) ("Sandoz's seeking ANDA approval and proposing draft labeling that will instruct how to engage in infringing uses constitute the affirmative steps required to show inducement.").

(5) Mylan Infringes All Asserted Claims

389. In sum, based on the testimony of Dr. Lisak, Dr. Grant, Dr. Sampson, and Dr. Gokel, the documentary evidence they referred to during their testimony, and Mylan's stipulations, Mylan's manufacture and sale of its proposed glatiramer acetate product would infringe each of the asserted claims.

(ii) Sandoz's Proposed Product Infringes Each of the Asserted Claims

390. Plaintiffs presented evidence at trial that Sandoz's proposed product meets each and every limitation of the asserted claims. (Sept. Tr. (Gokel) 413:22-415:15, 447:20-469:7; PTX 987 at 101-110.) Sandoz has contested infringement of only two claim limitations: copolymer-1 and test reaction. For the reasons set forth below, Sandoz's proposed product infringes each of the asserted claims.

(1) Sandoz's Product is Copolymer-1

391. From the beginning of this litigation up until almost the eve of trial, Sandoz did not dispute that its proposed generic Copaxone® product was copolymer-1. In its pretrial submissions, however, Sandoz raised for the first time an argument that its proposed product is not copolymer-1 because it does not have an amino acid molar ratio of approximately 6:2:5:1. Sandoz's argument is without merit.

392. As set forth above, Sandoz's ANDA provides molar fraction data for its proposed product. As Dr. Gokel testified at trial, and as can be seen in Figure 18 below, when Sandoz's molar fraction data and "6:2:5:1" are compared on the same scale, it is plain that Sandoz's molar ratio is approximately 6:2:5:1. (Sept. Tr. (Gokel) 417:14-421:16; PTX 987 at 90.) Dr. Gokel's testimony was unrebutted.

Figure 18

Sandoz Original ANDA Lot 077K7277

Amino Acid	6:2:5:1	6:2:5:1 (Scale = 1)	Lot 077K7277 (Scale = 1)		Scale = 14	
A	6	.43	.436	x 14	6.10	6
G	2	.14	.147	x 14	2.06	2
L	5	.36	.334	x 14	4.68	5
T	1	.07	.083	x 14	1.16	1
Scale	14	1	1		14	14

90

393. Contrary to what Sandoz has argued, the result is not different if the [redacted] is considered (even though Sandoz has not yet amended its ANDA to include the manufacturing process that results in these molar fractions). As Dr. Gokel testified, and as can be seen in Figure 19 below, the molar ratio in Sandoz's new lot is also

approximately 6:2:5:1. (Sept. Tr. (Gokel) 420:3-422:15; PTX 987 at 95.) This testimony was also unrebutted.

Figure 19

Sandoz New Lot 051M7282

Amino Acid	6:2:5:1	6:2:5:1 (Scale = 1)	Lot 051M7282 (Scale = 1)		Scale = 14	
A	6	.43	.427	x 14	5.98	6
G	2	.14	.136	x 14	1.90	2
L	5	.36	.344	x 14	4.82	5
T	1	.07	.093	x 14	1.30	1
Scale	14	1	1		14	14

95

394. Sandoz's proposed product therefore literally meets the limitation of "approximately 6:2:5:1" and is copolymer-1 within the meaning of the asserted claims.

395. Even if Sandoz's product did not literally meet the requirement of a molar ratio of "approximately 6:2:5:1," it would meet that requirement under the doctrine of equivalents.

396. As shown in Figure 20 below, the percent total difference in amino acid ratios between Sandoz's product and exactly 6:2:5:1 is 4.4%. (Sept. Tr. (Sampson) 546:21-547:22; PTX 988 at 3.) For the reasons discussed above with respect to Mylan's product, Sandoz's proposed product is equivalent to approximately 6:2:5:1.

Figure 20

	Exactly "6:2:5:1"	Exactly "6:2:5:1" (expressed as %)	Sandoz's Molar Fraction	Expressed as %
A Alanine	.429	42.9%	.427	42.7%
G Glutamic Acid	.143	14.3%	.136	13.6%
L Lysine	.357	35.7%	.344	34.4%
T Tyrosine	.071	7.1%	.093	9.3%
Total	1	100%	1	100%
				4.4% total difference

Molar fraction data taken from PTX 913 at MMT01630061

(2) Sandoz's Product Meets the Molecular Weight Limitations

397. Dr. Grant explained at trial why Sandoz's ANDA product meets the molecular weight limitations of each of the asserted claims. (Sept. Tr. (Grant) 265:2-268:3.) Sandoz did not offer any testimony to rebut Dr. Grant's conclusions.

(a) Average molecular weight limitations

398. Dr. Grant testified that Sandoz's method for determining the peak molecular weight values of its product involves using an appropriately calibrated suitable gel filtration column. (Sept. Tr. (Grant) 212:4-218:17; PTX 209 at SDZ00002017.)

399. Based on Dr. Grant's testimony and the peak molecular weight data in Sandoz's ANDA, Sandoz's proposed product meets the molecular weight limitations of claims 1 of the '808 patent and claim 1 of the '589 patent, which require a copolymer-1 having an average molecular weight of "about 5 to 9 kilodaltons;" claims 1 and 6 of the '847 patent and claims 1, 8, 9, 12, 23, 30, and 31 of the '539 patent, which require a copolymer-1 having an average molecular weight of "about 4 to about 9 kilodaltons;" and claim 10 of the '539 patent, which requires a copolymer-1 with an average molecular weight of "6.25 to 8.4 kilodaltons." (Sept. Tr.

(Grant) 223:20-225:2.)

(b) Copolymer-1 molar fraction limitations

400. Based on Dr. Grant's calculations, Sandoz's proposed product meets the molecular weight limitations of claims 1-3 of the '430 patent, which requires the copolymer-1 to have over 75% of its molar fraction within the molecular weight range of 2 and 20 kDa; claims 8 and 30 of the '539 patent, which require the copolymer-1 to have less than 2.5% of its molar fraction with molecular weights above 40 kDa; claims 9, 10, and 31 of the '539 patent and claim 8 of the '098 patent, which require that the copolymer-1 have over 75% of its molar fraction between the molecular weights of 2 and 20 kDa and less than 2.5% of its molar fraction with molecular weights greater than 40 kDa; claim 1 of the '476 patent, claim 1 of the '161 patent, and claim 1 of the '098 patent which require that the copolymer-1 have over 75% of its molar fraction between the molecular weights of 2 and 20 kDa and less than 5% of its molar fraction with molecular weights greater than 40 kDa. (Sept. Tr. (Grant) 233:23-235:2.)

(c) TFA copolymer-1 molar fraction limitations

401. Based on Dr. Grant's calculations, Sandoz's proposed product meets the molecular weight limitations of Claims 1-3 of the '430 patent, claim 1 of the '476 patent, and claim 1 of the '161 patent, which require that the TFA copolymer-1 that is made as a result of treatment of protected copolymer-1 with hydrobromic acid have over 75% of its molar fraction with molecular weights between 2 and 20 kDa. (Sept. Tr. (Grant) 239:11-240:8.)

(3) Sandoz's Process Meets the Process Limitations

402. With the exception of the "predetermined by test reaction" limitation, Sandoz has not disputed that the manufacturing process in its ANDA meets the process limitations of the asserted claims.

403. Based on Dr. Gokel's testimony and the information in Sandoz's ANDA, Sandoz's process meets the "reacting protected copolymer-1 with hydrobromic acid" limitation found in claim 1 of the '808 patent, claim 1 of the '589 patent, claims 1-2 of the '898 patent, claims 1-2 of the '430 patent, claim 1 of the '476 patent and claim 1 of the '161 patent; the "treating trifluoroacetyl copolymer-1" limitation found in claim 1 of the '808 patent, claim 1 of the '589 patent; claims 1-3 of the '898 patent, claims 1-3 of the '430 patent, claim 1 of the '476 patent, claim 1 of the '161 patent and claims 1 and 6 of the '847 patent; the "purifying" limitation found in claim 1 of the '808 patent, claim 1 of the '589 patent and claims 1 and 6 of the '847 patent; the "selecting a predetermined molecular weight profile" limitation of claims 1-3 of the '898 patent; and the "copolymer-1 fraction" limitations of claim 1 of the '161 patent and claim 1 of the '476 patent. (Sept. Tr. (Gokel) 349:4-350:18, 354:16-363:13, 447:20-469:7.)

(a) Sandoz's ANDA process meets the test reaction limitations

404. Sandoz's current ANDA, which comprises Sandoz's original ANDA from 2007 [redacted] sets forth a process for making copolymer-1 in which test reactions are used to predetermine the time and temperature of the reaction of protected copolymer-1 with HBr/acetic acid. At trial, Sandoz did not contest that the manufacturing process, as set forth in the current ANDA, meets the "predetermined by test reaction" limitation in the asserted claims.

405. "Predetermined by a test reaction" has been construed to mean "determined beforehand by a reaction carried out to determine results of varying reaction conditions." (D.I. 273, at 50.)

406. According to the current ANDA, in order to obtain a copolymer-1 that would meet the average molecular weight specification of 5,000 to 9,000 daltons, Sandoz ran the profile

runs described in paragraphs 306-309. (Sept. Tr. (Gokel) 424:12-425:15; PTX 214 at SDZ00000186.) These profiles runs are test reactions, as they were carried out to determine results of varying reaction conditions. (Sept. Tr. (Gokel) 425:22-24.)

407. The reaction conditions (*i.e.*, the time and temperature) from these test reactions were, in turn, applied to Sandoz's production batches. (Sept. Tr. (Gokel) 424:12-425:15; PTX 214 at SDZ00000186.) Thus, the time and temperature of the HBr/acetic acid reaction that is used to manufacture Sandoz's production batches were determined beforehand.

408. Sandoz therefore created production batches of copolymer-1 using an HBr/acetic acid reaction that took place for a time and at a temperature that were "determined beforehand by a reaction carried out to determine results of varying reaction conditions." (Sept. Tr. (Gokel) 423:1-4, 425:16-21.) Its current ANDA process therefore meets the "predetermined by test reaction" limitation in claims 1-2 of the '898 patent, claims 1-2 of the '430 patent, claim 1 of the '476 patent, and claim 1 of the '161 patent.

409. In addition, because the current Sandoz ANDA sets forth a time of 43-47 hours and a temperature of 20 ± 2°C, the particular time ("about 10-50 hours") and temperature ("about 20-28°C") limitations of claim 2 of the '898 patent and claim 2 of the '430 patent are met. (Sept. Tr. (Grant) 363:14-364:7; PTX 353 at SDZ00017631-32.)

(b) <u>The proposed process in Sandoz's Briefing Book meets the test reaction limitations</u>

410. To date, Sandoz has not filed an amended ANDA that makes any of the changes that were proposed in its Briefing Book. (PTX 913.) Thus, the current ANDA as filed with the FDA comprises the 2007 original ANDA [redacted] The Court, therefore, will only consider the current ANDA as filed with the FDA in determining infringement. *See Abbott Labs. v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed.

Cir. 2002) ("Because drug manufacturers are bound by strict statutory provisions to sell only those products that comport with the ANDA's description of the drug, an ANDA specification defining a proposed generic drug in a manner that directly addresses the issue of infringement will control the infringement inquiry.").

411. This conclusion is confirmed by the fact that during additional discovery ordered on the Briefing Book process, and during the trial itself, Sandoz and Momenta have continued to assert that their manufacturing process will change. In fact, Dr. Bishop testified at trial, without any documentary support, that Sandoz now intends to change the manufacturing process yet again so that the backup time and temperature model (as explained above at paragraphs 322-325 above) will be removed and that Sandoz will rely only on a backup viscometer. (Sept. Tr. (Bishop) 1105:12-25.)

412. Sandoz's expert Dr. Laird similarly testified that because the Sandoz process uses two viscometers, one has to be considered a backup, negating the need for the backup time and temperature model. Dr. Laird admitted, however, that the current batch record, which contains Sandoz's current manufacturing process, indicates that the second viscometer yields different readings than the first viscometer, and that the calculations necessary to use the second viscometer to determine when to stop the HBr/acetic acid reaction (assuming that such calculations even exist) are not contained in the batch record. (Sept. Tr. (Laird) 1163:2-1164:21.) Further, the batch record does not even refer to the second viscometer as a backup viscometer. (PTX 928 at MMT01707038.)

413. In light of this uncertainty surrounding Sandoz's ever-changing manufacturing process and in light of Federal Circuit precedent, the Court will use the process as currently submitted to the FDA to assess infringement. As concluded above, there is no dispute that the

current process in the Sandoz ANDA meets all the limitations.

414. Even if the Court were to assess infringement based on the process that Sandoz proposed in the Briefing Book, that process also has a step in which protected copolymer-1 is reacted with HBr/acetic acid for a time and at a temperature "determined beforehand by a reaction carried out to determine results of varying reaction conditions."

415. While the Briefing Book indicates that Sandoz has proposed an in-process control to monitor the progress of the HBr/acetic acid reaction, the batch records set forth the actual details of the process. (PTX 928 at MMT01707032-40.) These batch records must be submitted to the FDA as part of any future amendment to Sandoz's ANDA. (Sept. Tr. (Laird) 1157:11-14.)

416. The batch record sets forth two models for how to determine the time and temperature of the HBr/acetic acid reaction. These two models are considered part of the same manufacturing process. (Sept. Tr. (Laird) 1158:17-1159:11.) Under both models described in the Briefing Book and accompanying batch records, the time and temperature are predetermined by a test reaction.

417. The "viscometer" model comprises a table of temperatures and viscosity values. (Sept. Tr. (Gokel) 430:7-434:22; PTX 914 at MMT01630951-52; PTX 928 at MMT01707035.) These data are based on test reactions, as that term has been construed by the Court. (Sept. Tr. (Gokel) 436:18-439:10; PTX 923 at MMT01694006, 106-124.) Dr. Laird agreed that these data were obtained from test reactions. (Sept. Tr. (Laird) 1160:4-8.) The "time and temperature" model comprises a table of times and temperatures. (Sept. Tr. (Gokel) 435:14-436:3; PTX 914 at MMT01630954-55; PTX 928 at MMT01707036.) These data are also based on test reactions. (Sept. Tr. (Gokel) 436:18-439:10; PTX 923 at MMT01694006, 106-124.)

418. The temperature in both models is predetermined, as there is a pre-set temperature

target of 21°C, and each model contains a column that identifies particular temperatures in tenths of a degree. (Sept. Tr. (Gokel) 432:11-23, 435:14-436:3; PTX 914 at MMT01630954-55; PTX 928 at MMT01707035-36.)

419. Time is predetermined according to the viscometer model because there is a predetermined relationship between time and viscosity, so that no matter which model is used, the time has been determined beforehand. (Sept. Tr. (Gokel) 436:4-17.) Even if time is not literally predetermined in the viscometer model, the overall process of determining when to stop the HBr/acetic acid reaction in order to obtain a copolymer-1 having an average molecular weight of 7300 daltons is insubstantially different. *See Adams Respiratory Therapeutics*, 616 F.3d at 1293 ("The proper inquiry is whether the accused value is insubstantially different from the claimed value."); *Boehringer Ingelheim Vetmedica*, 320 F.3d at 1351 ("Under the doctrine of equivalents, a claim limitation not literally met may be satisfied by an element of the accused product if the differences between the two are 'insubstantial' to one of ordinary skill in the art.").

420. The time and temperature model, however, could be used for any batch, and therefore must be considered for infringement. There is no argument that the times in the time and temperature model have not been predetermined. (Sept. Tr. (Gokel) 436:9-12.)

421. Even if the time and temperature model were not considered in determining whether the viscometer model literally meets the "predetermined by test reaction" limitation of the claimed methods, determining when to stop the reaction in order to obtain a copolymer-1 having an average molecular weight of 7,300 daltons by using test reactions to predetermine a relationship between the temperature and viscosity and the time to stop the reaction is insubstantially different from using test reactions to predetermine a pre-set time to stop the reaction. In either case, a copolymer-1 having an average molecular weight of 7,300 daltons is

obtained.

422. Thus, the process that Sandoz has proposed in its Briefing Book meets the "predetermined by test reaction" limitation in claims 1-2 of the '898 patent, claims 1-2 of the '430 patent, claim 1 of the '476 patent, and claim 1 of the '161 patent, either literally or under the doctrine of equivalents.

423. In addition, because the Briefing Book process under either model targets a temperature of 21°C and can range only from 20.0°C to 24.0°C, the temperature limitation ("about 20-28°C") of claim 2 of the '898 patent and claim 2 of the '430 patent is met. Further, because the time and temperature model sets forth a range of times between 45.8 and 25.9 hours, the time limitation of "about 10-50 hours" of claim 2 of the '898 patent and claim 2 of the '430 patent is met.

(4) Sandoz Meets the Treatment Limitations

424. Based on Dr. Lisak's testimony, Sandoz's proposed product meets the "method of treating multiple sclerosis" limitation found in claim 1 of the '476 patent; the "administering to a subject in need thereof" limitation found in claim 1 of the '476 patent; the "pharmaceutically effective amount" limitation found in claim 1 of the '476 patent and claim 1 of the '161 patent; the "treatment of multiple sclerosis" limitation found in claim 1 of the '161 patent; the "suitable for treating multiple sclerosis" limitation found in claim 1 of the '539 patent; the "dose therapeutically effective to treat multiple sclerosis" found in claim 12 of the '539 patent; the "a method for treating a patient suffering from multiple sclerosis" found in claims 23, 30, and 31 of the '539 patent; the "administering to a patient in need thereof" limitation found in claims 23, 30, and 31 of the '539 patent; and the "suitable for treating multiple sclerosis" limitation found in claim 1 of the '098 patent. (Sept. Tr. (Lisak) 137:5-147:19; PTX 985 at 20.)

425. In addition, based on the stipulation entered into by Sandoz, Sandoz's proposed

product meets the limitations of "pharmaceutical composition" and "pharmaceutically acceptable excipient" in claims 12, 23, 30, and 31 of the '539 patent. (PTX 936.)

426. Finally, Sandoz will induce physicians to infringe the '476 and '539 patents should its ANDA be approved. Sandoz knew of those patents before filing its ANDA, as it filed a certification with the FDA and sent a notice letter to Teva specifically referencing the patents-in-suit, including the '476 and '539 patents. (*See* PTX 254 at SDZ00016843; Pretrial Order at ¶¶ 89-90, 94-95.) Sandoz's proposed product label will induce doctors to prescribe its ANDA product for treatment of multiple sclerosis and thereby induce infringement of claim 1 of the '476 patent and claims 23, 30, and 31 of the '539 patent. *See AstraZeneca LP*, 633 F.3d at 1060-61 ("The pertinent question is whether the proposed label instructs users to perform the patented method. If so, the proposed label may provide evidence of [the alleged infringer's] affirmative intent to induce infringement."); *see also Wyeth*, 703 F. Supp. 2d at 521 ("Sandoz's seeking ANDA approval and proposing draft labeling that will instruct how to engage in infringing uses constitute the affirmative steps required to show inducement.").

(5) Sandoz Infringes All the Asserted Claims

427. In sum, based on the testimony of Dr. Lisak, Dr. Grant, Dr. Sampson, and Dr. Gokel, the documentary evidence they referred to during their testimony, and Sandoz's stipulations, Sandoz's manufacture and sale of its proposed glatiramer acetate product would infringe each of the asserted claims.

VII. FINDINGS OF FACT AND CONCLUSIONS OF LAW RELATING TO DEFENDANTS' INDEFINITENESS AND ENABLEMENT DEFENSES

428. Over the course of this litigation Defendants have made two primary indefiniteness arguments. First, Defendants argued that a person of ordinary skill in the art would not be able to understand the meaning of the molecular weight claim terms. Second,

Defendants have argued that a person of ordinary skill in the art would not be able to determine whether a copolymer-1 sample met the claim limitations because the "standards and conditions" for molecular weight analysis were not identified in the patent specification.

429. The Court's Claim Construction Order largely disposed of both of these arguments. First, the Court held that the claim terms related to "average molecular weight" were amenable to construction, and construed "average molecular weight" to mean "peak molecular weight detected using an appropriately calibrated suitable gel filtration column." (No. 08-cv-7611, D.I. 273, No. 09-cv-8824, D.I. 194, Claim Construction Order at 40 & n.10); *Exxon Research & Eng'g Co. v. United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001) (finding that claims are indefinite only if reasonable efforts at claim construction prove futile). Second, the Court analyzed and rejected Defendants' "standards and conditions" indefiniteness argument. (Claim Construction Order at 31-36.)

430. At trial, Mylan did not pursue any indefiniteness theory. Sandoz did not pursue the argument that the failure to disclose specific "conditions" for the operation of the SEC column rendered the claims indefinite or not enabled. Rather, Sandoz pursued only the argument that the claims are invalid because the patent specification does not identify the molecular weight calibration "standards" or how to measure the molecular weights of such standards.

431. Sandoz has not argued that any asserted claims of the '898 patent are invalid as indefinite or not enabled. (Sept. Tr. (Scandella) 1224:13-21; Sept. Tr. (Wall) 1764:6-17.)

432. The bar for demonstrating that claims are invalid due to indefiniteness or lack of enablement is, however, set high. *Microsoft Corp. v. i4i Limited Partnership*, 131 S. Ct. 2238, 2246-47 (2011); *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1338-39 (Fed. Cir. 2008). The clear and convincing standard is a heightened standard of proof, and a defendant

raising an invalidity defense bears a "heavy burden of persuasion." *Microsoft Corp.*, 131 S. Ct. at 2246-47.

433. "When, as here, a party asserts invalidity of a patent and bases that assertion on evidence, including prior art references, that was before the patent examiner when he allowed the patent claims, the difficulty of overcoming the presumption of validity is greater than it would be if the evidence relied on was not before the examiner." *In re Omeprazole Patent Litigation*, 490 F. Supp. 2d 381, 500 (S.D.N.Y. 2007) (citing *Am. Hoist & Derrick Co. v. Sowa & Sons*, 725 F.2d 1350, 1358-60 (Fed. Cir. 1984)); *see also Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1367 (Fed. Cir. 2011).

434. Defendants have failed to carry their burden of proving indefiniteness or non-enablement by clear and convincing evidence. As set forth below, the evidence offered at trial further confirms what this Court has previously stated: "Sandoz and Mylan argue that every use of the term 'molecular weight' in the patent claims is indefinite. The Court disagrees." (Claim Construction Order at 16.)

A. Legal Principles—Definiteness

435. The determination of whether a claim term is amenable to construction, and therefore definite, is a matter of law. *See, e.g.*, *Kinetic Concepts, Inc. v. Blue Sky Med. Group*, 554 F.3d 1010, 1022 (Fed. Cir. 2009). To establish indefiniteness, Defendants must prove by clear and convincing evidence that the terms "average molecular weight" and "copolymer-1 having a molecular weight" cannot be construed in the context of the patents-in-suit. The critical question for indefiniteness is whether a person of skill in the art would understand the meaning of the claims. *Id*.

436. A claim is not indefinite merely because the meaning of the claim is not plain on its face. *Exxon Research & Eng'g Co.*, 265 F.3d at 1375. "If the meaning of the claim is

discernable, even though the task may be formidable and the conclusion may be one over which reasonable persons will disagree, [the Federal Circuit has] held the claim sufficiently clear to avoid invalidity on indefiniteness grounds." *Id.* Thus, only claims that are "insolubly ambiguous" even after the Court uses all tools at its disposal to try to construe the claims are invalid as indefinite. *See Source Search Techs., LLC v. LendingTree LLC*, 588 F.3d 1063, 1076 (Fed. Cir. 2009); *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d 1357, 1371 (Fed. Cir. 2008); *All Dental Prodx, LLC v. Advantage Dental Prods., Inc.*, 309 F.3d 774, 780 (Fed. Cir. 2002).

437. To satisfy Section 112's "definiteness requirement, the boundaries of the claim, as construed by the court, must be discernible to a skilled artisan based on the language of the claim, the specification, and the prosecution history, as well as her knowledge of the relevant field of art." *Power-One, Inc. v. Artesyn Techs., Inc.*, 599 F.3d 1343, 1350 (Fed. Cir. 2010); (Claim Construction Order at 5.) In addition, "the fact that some experimentation may be necessary to determine the scope of the claims does not render the claims indefinite." *Exxon Research & Eng'g Co.*, 265 F.3d at 1379; Claim Construction Order at 5.

B. Legal Principles—Enablement

438. A patent claim is invalid for lack of enablement only if the claimed invention cannot be practiced without "undue experimentation" by a person of ordinary skill in the art. *Monsanto Co. v. Scruggs*, 459 F.3d 1328, 1337-38 (Fed. Cir. 2006); *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988). What constitutes undue experimentation, as explained by the courts, "requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art." *In re Wands*, 858 F.2d at 737.

439. The Federal Circuit has made clear that a patent specification is not a product specification. *Koito Mfg. Co. Ltd. v. Turn-Key-Tech, LLC*, 381 F.3d 1142, 1156 (Fed. Cir.

2004). Although a patent specification must provide an enabling disclosure, a claim does not fail the enablement requirement simply because details that would be known and available to those of skill in the art are not set forth in the patent specification. *Singh v. Brake*, 317 F.3d 1334, 1345 (Fed. Cir. 2002); *Ajinomoto Co., Inc. v. Archer-Daniels-Midland Co.*, 228 F.3d 1338, 1345 (Fed. Cir. 2000); *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) (holding that the patent was enabled because the methods were known in the art, and stating that "a patent need not teach, and preferably omits, what is well known in the art.").

440. Determining whether required experimentation is "undue" requires consideration of the technology at issue and the level of skill in the art. *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1365 (Fed. Cir. 2006) (finding claims to a vaccine were enabled where the skill level in the art was high, and agreeing with the BPAI that "the mere fact that the experimentation may have been difficult and time consuming does not mandate a conclusion that such experimentation would have been considered 'undue' in this art."); *Monsanto Co.*, 459 F.3d at 1338 (specific DNA sequence was not required for enablement in part because of the level of skill in the art); *In re Wands*, 858 F.2d at 740 (weighing the high level of skill in the art in holding that undue experimentation would not be required).

441. As a matter of law, a person of ordinary skill in the art is deemed familiar with *all* pertinent prior art. *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986); *In re Omeprazole Patent Litig.*, 490 F. Supp. 2d at 511.

442. Furthermore, the Federal Circuit has held that evidence regarding work done in a

patentee's laboratory is insufficient as a matter of law to show lack of enablement where there is no evidence that the persons performing the work were persons of ordinary skill in the art. *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998) ("Because it is imperative when attempting to prove lack of enablement to show that *one of ordinary skill in the art* would be unable to make the claimed invention without undue experimentation, . . . CellPro's evidence concerning [the inventor's] subsequent work is insufficient as a matter of law.").

443. In determining whether a claim is enabled, courts have looked to the following factors, known as the "*Wands*" factors:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d at 737.

C. Findings of Fact on Definiteness and Enablement

(i) A Person of Ordinary Skill is Highly Skilled in SEC

444. The testimony by the experts at trial was unanimous on at least one issue: that the level of skill in the art of the patents-in-suit was (and is) high. Particularly relevant to this analysis, all experts agree that a person of ordinary skill would have specific experience and skills in size exclusion chromatography. (*See* Sept. Tr. (Grant) 189:22-190:6; PTX 986 at 3 (having an "advanced degree or equivalent in a chemical or biological discipline, and significant experience in the synthesis or characterization of polymers, including proteins or synthetic peptides"); Sept. Tr. (Scandella) 1190:15-20, 1300:20-1301:9 ("a Ph.D. in chemistry, biochemistry or related field with a minimum of three years of experience in chromatography and specifically in size exclusion chromatography of macromolecules."); Sept. Tr. (Zeiger) 809:10-811:15; DTX 4030 at 4 (definition includes "extensive experience in the synthesis,

fractionation, and characterization of polymers, such as their hydrodynamic and structural properties, as applied to proteins, synthetic peptides and/or polydisperse peptide mixtures, as well as experience in the determination of the molecular weight distribution and average molecular weights of such polymers by methods such as size exclusion chromatography (SEC), and an understanding of how the standards and conditions used in the molecular weight determination affect the results obtained.").

(ii) A Person of Skill Could Accurately Determine the Molecular Weight of Copolymer-1 in 1994

445. In 1994, a person of skill in the art could have determined the molecular weight of a copolymer-1 sample using SEC based on the teachings in the patents-in-suit without undue experimentation. (Sept. Tr. (Grant) 1422:9-14.) Indeed, Mylan's expert witness, Dr. Hurwitz, admitted that in 1994, a person of ordinary skill in the art could have used SEC on a sample of copolymer-1 to determine its peak molecular weight:

Q. The person of ordinary skill in 1994 could perform a measurement using SEC on a sample of copolymer-1 to determine the peak molecular weight, correct?
A. Yes.

(PTX 959 (Hurwitz Dep.) at 131:12-16.)

446. In order to accurately measure the molecular weight of copolymer-1, a person of skill in the art could have used either self-standards or universal calibration. (Sept. Tr. (Grant) 1399:18-1400:13; PTX 990 at 2.) Both techniques were well-known to persons of skill in the art in 1994.

(1) Self-Calibration Was Known in 1994

447. For conventional SEC, it was known in 1994 that in order to accurately correlate the retention time of the molecules coming out of an SEC column with their molecular weights, the column must be calibrated using standards with the same hydrodynamic characteristics as the

sample being measured. (Sept. Tr. (Grant) 1412:6-1413:16; Sept. Tr. (Scandella) 1314:15-1316:24; PTX 961 (Kota Dep.) 18:3-14; PTX 962 (B. Rao Dep.) at 75:6-76:10, 78:14-80:5; PTX 973 (Venkataraman Dep.) at 108:20-109:23; PTX 974 (Wallingford Dep.) 146:9-149:7; PTX 317 at MYL0000111; PTX 553 at 72.)

448. A person of ordinary skill in the art in 1994 would have understood that the polypeptides in copolymer-1 are not globular. (Sept. Tr. (Grant) 1425:12-23; PTX 970 (Svec Dep.) at 395:21-395:24, 396:16-397:8, 397:11-397:17, 397:24-398:15.) For this reason, a person of skill in the art would have understood that globular protein standards do not have the same hydrodynamic characteristics as copolymer-1 and would therefore be inappropriate for use in conventional calibration for copolymer-1, as they would not provide an accurate molecular weight. (Sept. Tr. (Grant) 272:19-273:25, 1399:8-17; PTX 970 (Svec Dep.) at 394:23-395:3, 398:16-398:25.)

449. Instead of globular proteins, in 1994, a person of skill in the art could have used self-standard calibration to accurately determine the peak molecular weight and molecular weight distribution (*e.g.*, the percentage of molecules between 2 and 20 kilodaltons or over above 40 kilodaltons) of a copolymer-1 sample. (Sept. Tr. (Grant) 1421:19-24, 1421:25-1422:8.)

450. Self-standards are standards made from the same material as the sample being measured, and therefore would, by definition, have the same hydrodynamic volume-to-molecular weight characteristics as the sample being measured. (Sept. Tr. (Grant) 1399:23-1400:13.) Dr. Scandella spent significant time at trial discussing possible shapes of copolymer-1 (*see* Sept. Tr. (Scandella) 1202:23-1205:19, 1229:16-24), but that testimony was irrelevant to the use of self-standards.

451. Self-standard calibration had been thoroughly described in the scientific literature

by 1994. For example, Billingham 1977 states that "[t]he most obvious method is to inject into the columns a series of monodisperse *standards of the polymer under test*" and that "[d]irect calibration with the polymer under test can be achieved by *using narrow distribution fractions of the polymer*." (PTX 514 at 210-11 (emphasis added); Sept. Tr. (Grant) 1414:8-1415:17.)

452. There are two ways to obtain self-standards: one is to use as standards whole batches of the polymer of interest having different molecular weights ("whole polymer" self standards), and the other is to use narrower fractions of the polymer sample of interest ("fractionated" self standards). (Sept. Tr. (Grant) 1399:23-1400:13.) Both are described in more detail below.

(a) Whole Polymer Self-Standards Were Known in 1994

453. The whole polymer self-standard method involves taking whole batches of the polymer of interest, each batch having a different molecular weight, and determining the molecular weights of the batches by independent (non-SEC) methods. (Sept. Tr. (Grant) 1401:9-11, 1418:7-15.)

454. The whole polymer self-standard method was described in the literature well prior to 1994. (Sept. Tr. (Grant) 1401:9-11; 1418:7-1420:20; PTX 514 at 211; PTX 566 at 37.) For example, Billingham 1977 describes two different methods of calibration using whole polymer standards in a section entitled "Calibration with Whole Polymer." (PTX 514 at 212-13; Sept. Tr. (Grant) 1401:9-11.) Similar methods are also described in Barth 1991, which includes two sections entitled "Calibration Using Polydisperse Standards of Known Molecular Weight Averages" and "Calibration Using Standards of Known Molecular Weight Distribution." (Sept. Tr. (Grant) 1419:13-1421:3; PTX 566 at 37-44.)

455. In the case of copolymer-1, a person of skill in the art in 1994 could have made

whole batches of copolymer-1 to use as self-standards, because the patents-in-suit teach how to make copolymer-1 of varying molecular weights. These batches could then be used as molecular weight standards. (PTX 1, col. 4:59-65; Sept. Tr. (Grant) 1401:19-1402:4; DTX 4022 (Varkony Dep.) at 252:4-13, 252:25-253:6, 257:17-22.) Dr. Sampson explained at trial that by varying the time and temperature of the HBr/acetic acid reaction step in the synthesis of copolymer-1, the molecular weight of the resulting copolymer-1 can be controlled. (Sept. Tr. (Sampson) 1641:6-1642:8; PTX 992 at 6-7.)

(b) Fractionated Self-Standards Were Known in 1994

456. The fractionated self-standard method involves taking a mixture of the substance of interest and separating it into smaller portions, or fractions, that can be used as calibration standards. (Sept. Tr. (Grant) 187:8-14.)

457. The fractionated self-standard method had been fully described in the literature prior to 1994. (Sept. Tr. (Grant) 1400:16-18.) For example, Billingham 1977 states that "[d]irect calibration with the polymer under test can be achieved by using narrow distribution fractions of the polymer, prepared either by preparative fractionation or by preparative scale GPC." (Sept. Tr. (Grant) 1414:12-1418:6; PTX 514 at 211-12.)

458. Fractionation of copolymer-1 into smaller portions of varying molecular weight is described in the patents-in-suit. The patent describes fractionation of copolymer-1 by running a sample through an SEC column and collecting the fractions as they exit the column. (PTX 1, col. 2:57-3:2; Sept. Tr. (Grant) 1400:16-1401:8, 1402:5-9; Sept. Tr. (Scandella) 1322:20-1324:7.) Fractionation was well known in the art in 1994. (Sept. Trial Tr. (Grant) 1400:16-18; (Zeiger) 866:11-20; 894:23-895:14.)

459. Each of the resulting fractions will have a different molecular weight, which can be independently measured so that the fractions can be used as calibration standards. (Sept. Tr.

(Grant) 1402:10-24.)

(c) Known Methods Existed in 1994 to Measure the Molecular Weight of Self-Standards

460. Once self–standards—whether whole or fractionated—are made, a person of skill in the art would have measured their molecular weights by an independent (non-SEC) method. (Sept. Tr. (Grant) 205:6-10, 1402:10-18.) At least some of these methods are known as absolute molecular weight methods. (Sept. Tr. (Grant) 1416:14-17.)

461. The methods available in 1994 for measuring the molecular weights of self-standards included, *e.g.*, multi-angle light scattering, viscometry (a.k.a. "viscosimetry"), ultracentrifugation, and mass spectrometry. (Sept. Tr. (Grant) 1402:19-1403:2; Sept. Tr. (Scandella) 1318:2-8.)

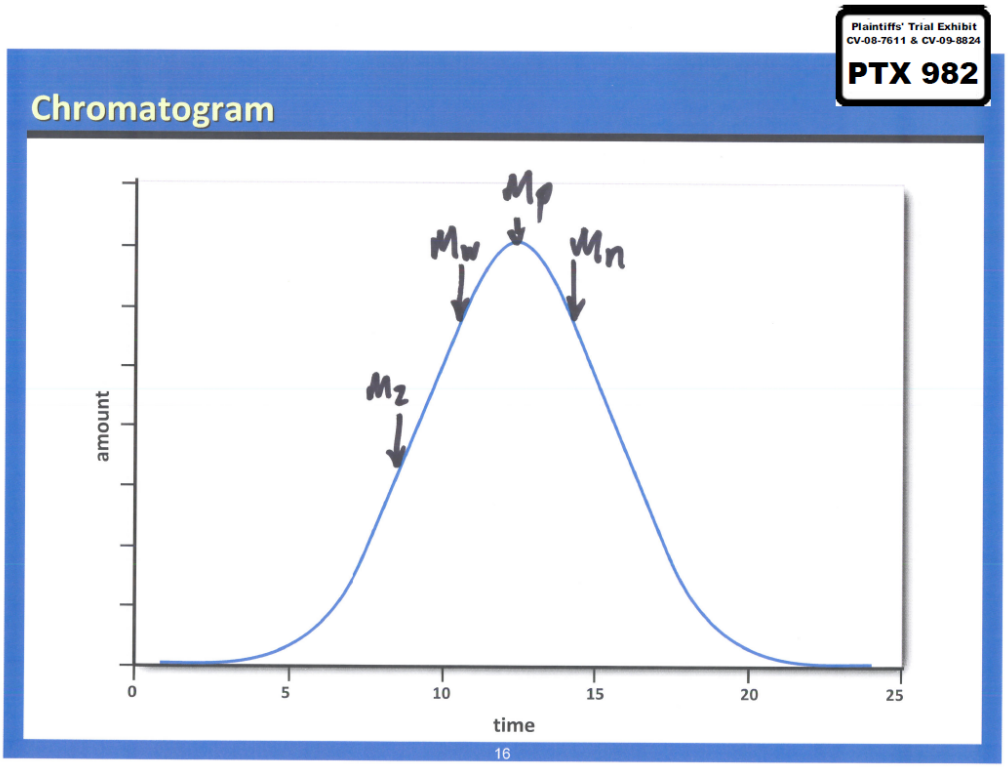
(d) Known Methods Existed in 1994 to Create An Accurate Calibration Curve Based on Self-Standards

462. Once the molecular weights of the self-standards had been measured, a person of skill in the art would use them to calibrate the SEC column by running them through the column, recording the times at which they exit the column, and then creating a calibration plot to correlate their molecular weights to their retention times. (Sept. Tr. (Grant) 1402:10-18.)

463. If self-standards were used for calibration, their average molecular weights could vary depending on the absolute method used to determine the molecular weight of the standard (*e.g.*, light scattering could measure a weight average molecular weight, while osmometry could measure a number average molecular weight). The different average molecular weight values provided by the various techniques would correspond to different retention times along the chromatogram for the sample. (Sept. Tr. (Grant) 1404:7-20; Sept. Tr. (Scandella) 1326:19-1327:16.) For example, if these various molecular weights are mapped out on a chromatogram

shaped as in PTX-982, the z-average molecular weight (Mz) would come out first (because it is the highest value and larger molecules exit the size exclusion column first), then the weight average molecular weight (Mw), followed by the peak average molecular weight (Mp) at the peak of the chromatogram, and then the number average molecular weight (Mn), after the peak (because it is generally the smallest of the "average" values), as shown below. (PTX 982; Sept. Tr. (Scandella) 1325:2-1326:18; Sept. Tr. (Grant) 1404:23-1405:13.)

Figure 21



464. The only technical difficulty with self standards identified by Sandoz's expert Dr. Scandella is that the different average molecular weight values measured by the different absolute measurement methods for the standards would result in different calibration curves, which would in turn lead to different determined molecular weights for the sample depending on which calibration curve was used. (Sept. Tr. (Scandella) 1272:3-25; DTX 3581 at 16.) On cross-examination, however, Dr. Scandella admitted that the demonstrative exhibit he presented

to the Court to explain this alleged discrepancy did not accurately depict the time associated with the measured molecular weight of the standard (*i.e.*, the time along the chromatogram for the self standard that would correlate with the measured average molecular weight for the standard). Although he agreed that each different type of measured average molecular weight for a standard would be associated with a *different retention time*, he admitted that his demonstrative depicted all of the different average molecular weights as being associated with the *same retention time*. (Sept. Tr. (Scandella) 1326:24-1327:21.) When confronted with this discrepancy, Dr. Scandella testified that his demonstrative was "not intended to be actual data." (Sept. Tr. (Scandella) 1327:24-25.)

465. Even though he testified regarding the differences between types of measured average molecular weight for self-standards, Dr. Scandella admitted that he does not have any experience working with polydispersed mixtures of polypeptides such as copolymer-1. (Sept. Tr. (Scandella) 1298:25-1299:7.) Dr. Scandella testified at his deposition that he had never done any SEC analysis of synthetic polypeptides. (Sept. Tr. (Scandella) 1299:20-1300:7.) Further, Dr. Scandella has no publications concerning the molecular weight of a protein using SEC. (Sept. Tr. (Scandella) 1300:8-12.)

466. Dr. Grant explained why Dr. Scandella's demonstrative exhibit was inaccurate. (Sept. Tr.(Grant) 1403:14-1404:20.)

467. As Dr. Grant testified, despite the potential difference in the average molecular weight (and hence the corresponding retention time) obtained using different absolute measurement techniques, it was well known in 1994 how to appropriately apply the different measured average molecular weights obtained using different methods to get an appropriate calibration curve that would provide an accurate molecular weight. (Sept. Tr. (Grant) 327:9-16.)

The process of obtaining a single accurate calibration curve from the measured molecular weights of self-standards was described extensively in the literature. (Sept. Tr. (Grant) 1403:3-13.) The literature provided numerous examples of procedures that could have been used to resolve calibration curves produced by different absolute molecular weight measurement techniques into a single calibration curve. (Sept. Tr. (Grant) 1408:25-1409:4.)

468. For example, for fractionated self-standards, Billingham 1977 describes ways to calculate the peak molecular weight of the self standards such that it can be accurately applied at the peak time. Dr. Grant explained that this means that "since a number average or a weight average is not going to have a time associated with it that's equal to the peak, you have to do some calculation or adjustment to be able to find what the accurate molecular weight at the peak." (Sept. Tr. (Grant) 1414:22-1417:3; PTX 514 at 211.) Dr. Grant also explained that a paper from the early 1970s cited by Billingham 1977 describes "several different types of methods that had already been developed by that time to do this adjustment, this calculation of the peak molecular weight from other types of average molecular weights" and that mathematical treatments that could be used to convert number average or weight average molecular weights into peak molecular weights were described in the literature in 1994. (Sept. Tr. (Grant) 1417:4-1418:6; PTX 514 at 211.)

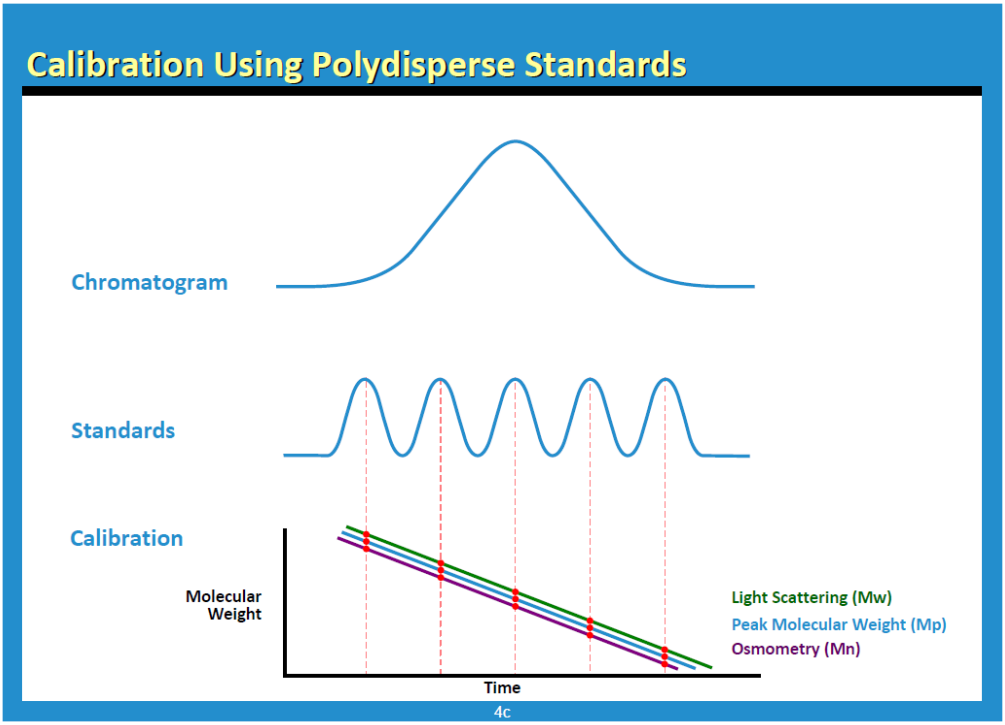
469. Additionally, Barth 1991 describes a variety of methods for generating calibration curves using polydisperse self-standards. (PTX 566 at 37-41.) Dr. Grant explained that Barth 1991 describes "a process that allows you to determine the accurate molecular weight at the peak for constructing a valid calibration curve" because "Mn and Mw are average molecular weights that can be determined by absolute methods" and "they do not correspond to molecular weights at the same time as the peak." (Sept. Tr. (Grant) 1419:13-1421:3; PTX 566 at 37.)

470. Dr. Grant further explained that Billingham 1977 and Barth 1991 represent only a very small part of the literature that was available in 1994 describing the processes for generating valid calibration curves and that "in fact there are well described and valid and effective methods to take calibration curves that may be constructed from different types of average molecular weights and resolve them into a single calibration curve, so that in fact in the end you only had a single valid calibration curve, and gives you an accurate molecular weight at the peak of your measuring." (Sept. Tr. (Grant) 1421:4-18.)

471. Dr. Grant presented a demonstrative to explain this technique described in the literature for applying different average molecular weight results from different techniques to generate a single valid calibration curve. (Sept. Tr. (Grant) 1406:1-1409:11; PTX 990 at 4a-i.) Dr. Grant presented an illustrative chromatogram of five broad self-standards, such as copolymer-1 self-standards, and a calibration curve based on the peak molecular weight times of the self-standards. (Sept. Tr. (Grant) 1406:1-17; PTX 990 at 4a.)

472. Dr. Grant explained that one would get different calibration curves if the different average molecular weights for the standards obtained through different absolute molecular weight measurement techniques were assigned to the same, *e.g.*, peak, retention time. This occurs because, as shown in his example, one technique, light scattering, gives a higher average value (a "weight" average (Mw)) than the peak average value, while a second technique, osmometry, gives a lower average value (a "number" average (Mn)) than the peak average value, but the weight average and number average values are being (erroneously) applied at the *same time* (the "peak" time). (Sept. Tr. (Grant) 1406:18-25,1407:7-13; PTX 990 at 4c.)

Figure 22



473. Dr. Grant explained that an adjustment was described extensively in the pre-1994 literature that addressed this issue. This adjustment would allow the different average molecular weights to be applied at the correct time. Such an adjustment—calculating the molecular weight of the standard at the peak so that it could be accurately applied at the peak time or appropriately applying the measured average molecular weight of the standard at its appropriate time—would cause the theoretically different calibration curves to be merged into a single accurate calibration curve. (Sept. Tr. (Grant) 1406:25-1407:6; PTX 990 at 4c-i.)

474. Dr. Grant demonstrated how a calibration curve based on weight average molecular weight (which is a larger value than the peak molecular weight value and therefore corresponds to a time to the left of the peak) of self standards could be adjusted. (Sept. Tr. (Grant) 1407:20-1408:8; PTX 990 at 4d.) Similarly, Dr. Grant demonstrated how a calibration

curve based on number average molecular weight value (which is smaller than the peak molecular weight value and therefore corresponds to a time to the right of the peak) of self-standards is adjusted. (Sept. Tr. (Grant) 1408:9-24; PTX 990 at 4f.) Dr. Grant testified without rebuttal that the adjustment would, in effect, move the weight average molecular weights to earlier times, *i.e.*, to the left (because larger molecules come out of the size exclusion column before smaller molecules). This would have the effect of sliding the light scattering calibration curve to the left. (Sept. Tr. (Grant) 1406:18-1407:6.) Similarly, the adjustment would have the effect of moving the osmometry curve to later times, *i.e.*, to the right. (Sept. Tr. (Grant) 1407:7:1408:24.) The adjustments are shown in the graphs below:

Figure 23

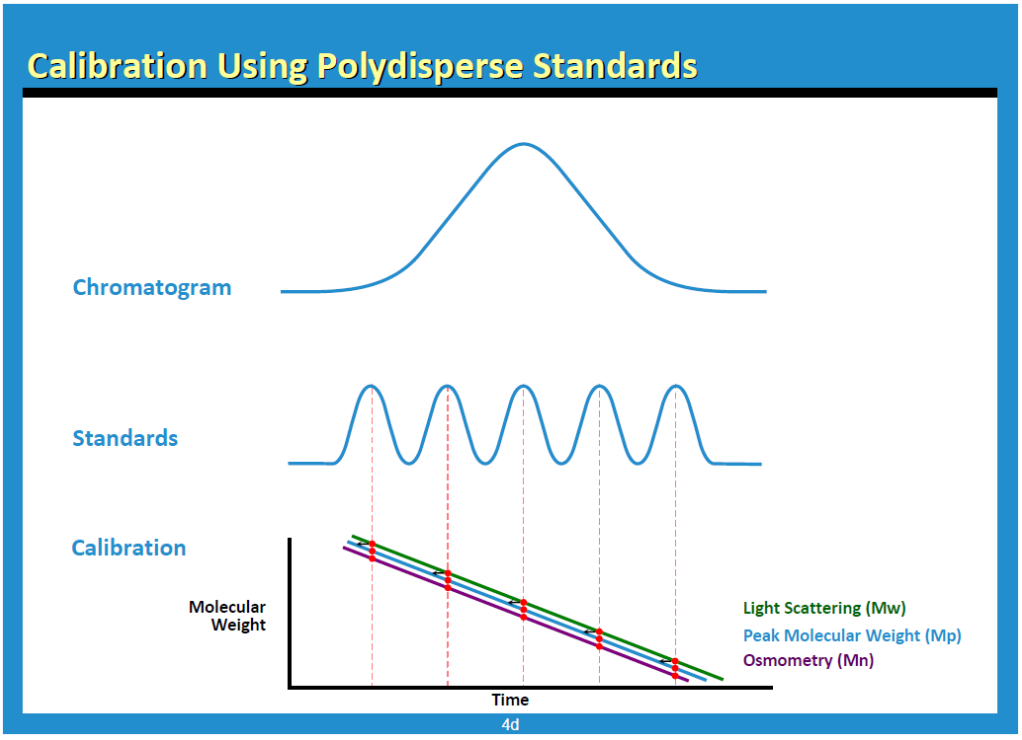
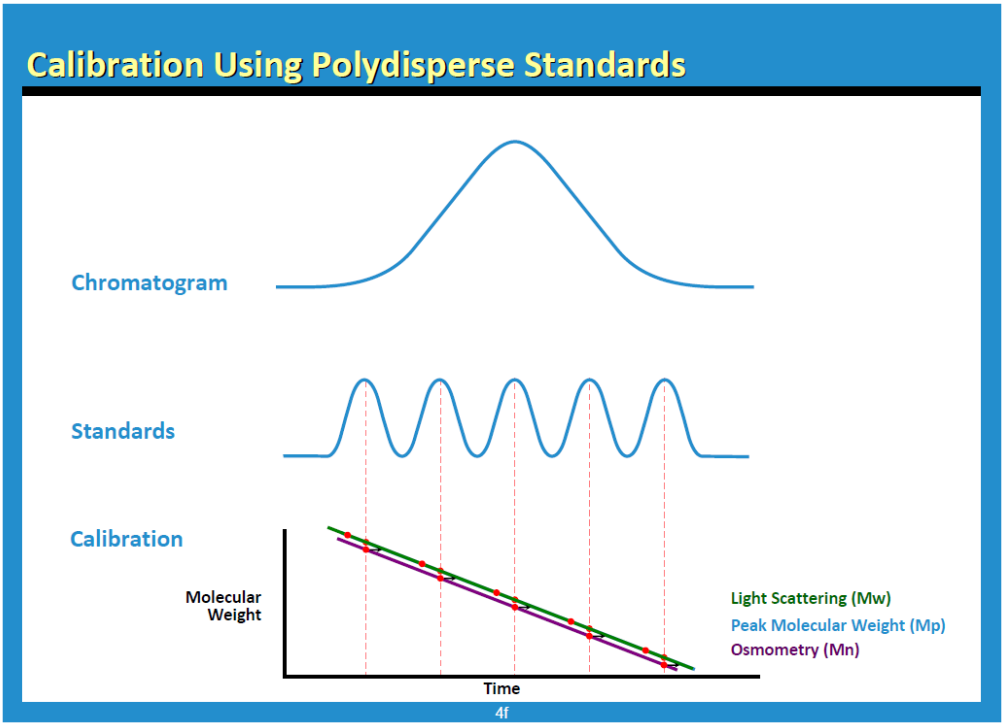


Figure 24

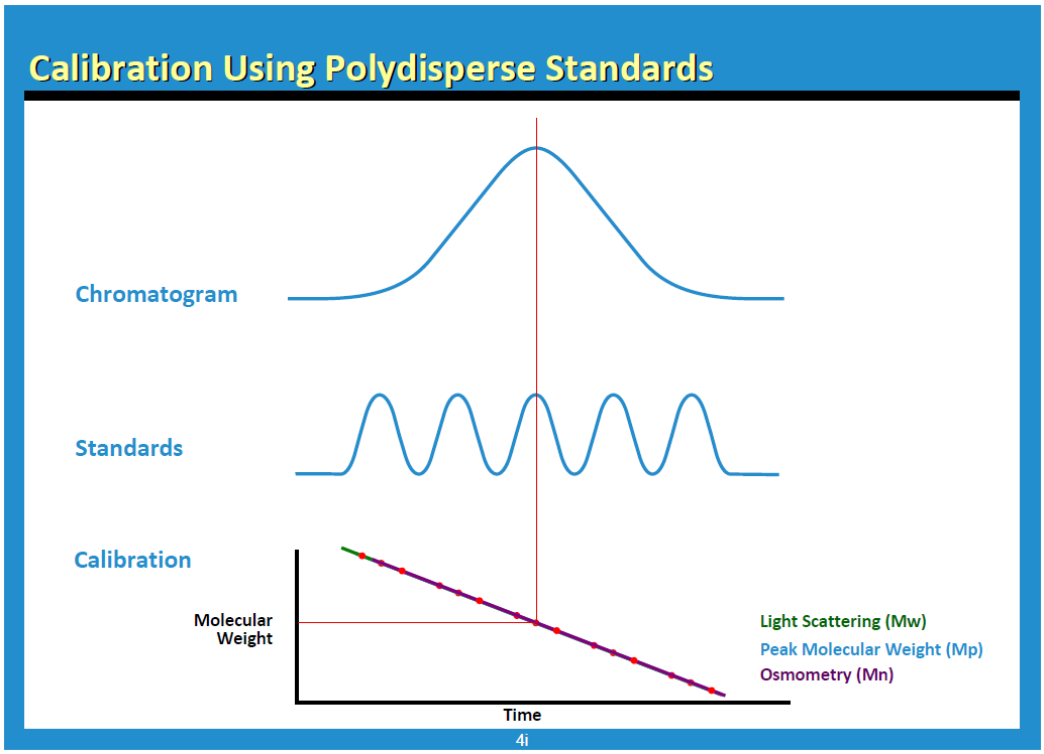


475. As explained by Dr. Grant, "the end result is that all three calibration curves become one." (Sept. Tr. (Grant) 1408:17-18.) Dr. Grant further explained how the single calibration curve could be used to obtain an accurate molecular peak molecular weight for a sample:

> At the end of the day, what this means is that you in fact do not have three different calibration curves from which you have to choose which one to use. You in fact have only a single calibration curve that gives you only a single accurate value for the peak of the chromatogram. . . . You locate the time of the peak, come down, find that time on your calibration curve, and you go over and read the molecular weight.

(Sept. Tr. (Grant) 1409:5-16; PTX 990 at 4i.)

Figure 25



476. Dr. Scandella agreed that techniques for correctly applying the measured average molecular weights of the standards at the correct retention time could have been available in 1994, but that he had not "looked at that recently." (Sept. Tr. (Scandella) 1328:7-16.)

(e) Teva Used Copolymer-1 Self-Standards to Determine the Molecular weight of Copolymer-1 Beginning in 1987

477. By August 1987, very early in its involvement in the copolymer-1 project, Teva had developed an effective method for accurately determining the molecular weight of copolymer-1. (Sept. Tr. (Grant) 1450:15-18, 1451:23-25, 1462:18-23; DTX 3275.)

478. Teva's 1987 method used size exclusion chromatography in which a Superose-12 column was calibrated using copolymer-1 whole polymer self-standards whose molecular weights had been determined by viscometry. (Sept. Tr. (Grant) 322:9-324:11, 1450:15-18,

1451:23-25, 1452:1-13; Sept. Tr. (Scandella) 1307:22-1308:2; Sept. Tr. (Wall) 1828:21-1829:5; DTX 3275 at TEV000304999-5000.)

479. Teva had no difficulty in deciding to use size exclusion chromatography to determine the molecular weight of copolymer-1 or in deciding to use copolymer-1 self-standards to calibrate its columns. (DTX 4022 (Varkony Dep.) at 252:18-22, 252:24.) Significantly, no evidence was presented at trial that anyone working at Teva in 1987 on the measurement of the molecular weight of copolymer-1 had the credentials or experience of a person of ordinary skill in the art as defined by the experts in this case. (Sept. Tr. (Scandella) 1301:10-13; DTX 4016 (Gad 11/10/2009 Dep.) at 12:10-13.) In particular, there was no evidence that any Teva scientist in 1987 had any experience with SEC. Despite this, development of the calibration method only took Teva a matter of several weeks. (DTX 4022 (Varkony Dep.) at 110:2-9.)

480. Teva recognized from the beginning that globular protein standards were inappropriate for determining the molecular weight of copolymer-1, because they resulted in molecular weights that were several times higher than the molecular weights obtained by other methods. (Sept. Tr. (Grant) 321:13-322:8, 1498:9-13, 1454:18-21, 1565:2-9, 1565:23-1566:9; DTX 3275 at TEV000304994-95; DTX 3510 at TEV001116321.)

481. Teva also recognized the reason for this inaccuracy: that proteins have a different hydrodynamic volume to molecular weight relationship than copolymer-1 molecules. (Sept. Tr. (Grant) 1565:2-9, 1565:23-1566:9; DTX 4022 (Varkony Dep.) at 63:20-64:5; DTX 3510 at TEV001116321.)

482. Teva used protein standards to test the performance and suitability of its size exclusion columns, but it did not use them to calibrate its columns for the purpose of determining molecular weight. (Sept. Tr. (Grant) 1450:24-1451:22, 1453:20-1454:17; DTX 4022 (Varkony

Dep.) at 62:24-63:2, 63:4-8, 63:10-16, 63:18-64:14, 64:17-21, 64:23-65:2; DTX 3510 at TEV001116321-22.)

483. In fact, Teva's internal documents make clear that any references to proteins being used for molecular weight calibration instead of "system suitability" were in error. (Sept. Tr. (Scandella) 1308:23-1309:22; DTX 3510 at TEV001116322.)

484. In November 1992, Teva began using copolymer-1 self-standards whose molecular weights had been determined by a technique known as multi angle laser light scattering, or MALLS. The copolymer-1 self-standards were batches of copolymer-1 that had been made for the purpose of being calibration standards by adjusting the reaction time and temperature of the debenzylation step in the process of synthesizing copolymer-1. (DTX 1701; DTX 4022 (Varkony Dep.) at 58:4-16.)

485. In June 1995, Teva submitted its original NDA to the FDA for approval. (Sept. Tr. (Grant) 1462:24-1463:4; Sept. Tr. (Wall) 1829:6-9.) Teva's Copaxone® NDA relied on copolymer-1 self standards for the molecular weight determination of Copaxone® batches, and the FDA ultimately approved Teva's NDA to market Copaxone® on that basis. (Sept. Tr. (Grant) 1462:24-1463:4.)

486. None of the details of the development of Teva's particular molecular weight determination method were publicly available to persons of skill in the art in 1994.

(2) Universal Calibration

487. In addition to self-standards, a person of skill in the art in 1994 could also have used universal calibration to accurately measure the peak molecular weight and molecular weight distribution (*e.g.*, the percentage of molecules between 2 and 20 kilodaltons or above 40 kilodaltons) of a sample of copolymer-1. (PTX 970 (Svec Dep.) at 320:2-7, 326:14-327:10, 320:22-321:10, 382:8-13, 384:23-385:6, 385:8-19; Sept. Tr. (Grant) 1430:8-1431:23.)

488. According to the theory of universal calibration, the molecular weight values obtained from size exclusion chromatography should not be dependent on the type of standards used for calibration. (PTX 970 (Svec Dep.) at 356:2-8.) Unlike conventional size exclusion chromatography, universal calibration does not require the calibration standards to have the same hydrodynamic volume-to-molecular weight relationship as the sample, because it uses a different physical property (intrinsic viscosity) to allow a correlation of the size of molecules exiting the column to their molecular weight. (Sept. Tr. (Grant) 208:14-20, 1400:6-15.)

489. Universal calibration has been known since the late 1960s. By 1994, it was well described in the literature. There was extensive literature on universal calibration and a very large number of studies that showed that it worked quite well for a variety of different types of polymers. (PTX 970 (Svec Dep.) at 296:16-22; Sept. Tr. (Grant) 1401:15-18, 1423:11-1430:7; PTX 514 at 213-17; PTX 553 at 73-76.) Furthermore, the ability to measure intrinsic viscosity was routine for persons of skill in the art in 1994. (PTX 970 (Svec Dep.) at 296:23-297:6.)

490. A person skilled in the art in 1994 could have used the available scientific literature to set up and carry out universal calibration in order to determine the molecular weight of copolymer-1 without significant experimentation. (Sept. Tr. (Grant) 1431:24-1432:11.)

491. Sandoz's expert Dr. Frantisek Svec, who was acknowledged by Sandoz's Dr. Scandella to be an expert in the use of universal calibration, agreed that universal calibration could be used to obtain accurate molecular weight results for a sample, and further that universal calibration could be used to obtain accurate molecular weights for copolymer-1:

> Q. So in your opinion a person of skill in the art could take a copolymer-1 sample and determine an accurate molecular weight?
> A. Yes. Take a sample and determine the molecular weight.

(PTX 970 (Svec 05/21/2010 Dep.) at 388:8-12; Sept. Tr. (Scandella) 1332:17-1334:13.)

492. Dr. Scandella admitted that he has never performed universal calibration. (Sept. Tr. (Scandella) 1332:17-23.) Dr. Svec has experience and expertise actually performing universal calibration. (Sept. Tr. (Scandella) 1333:1-19.) Thus, the only evidence supports the conclusion that universal calibration can be used to accurately measure the molecular weight of copolymer-1.

493. Natco also believed that universal calibration could be used to measure the molecular weight of glatiramer acetate, and, indeed, Mylan has used universal calibration to report molecular weight values for copolymer-1 to the FDA. In particular, Mylan relied on an article from 1967, Z. Gallot-Brubisic et al., "Universal Calibration for Gel Permeation Chromatography, J. Polymer Science, Polymer Letters Edition (1967), to support the validity of the method. (PTX 963 (B. Rao 6/30/2010 Dep.) at 135:15-20, 136:19-137:3; Sept. Tr. (Owens) 601:24-603:1, 603:21-605:4; DTX 1411 at MYL0150490-91.) [redacted]

494. The trial record clearly shows that both self-calibration and universal calibration were available to persons of skill in the art of the patents in suit in 1994; that these techniques were well-described in the scientific literature; and and that they could have been used to accurately determine the molecular weight of copolymer-1 samples.

D. Conclusions of Law Concerning Definiteness

(i) The Patent Claim Terms Are Amenable to Construction

495. A claim is not indefinite merely because the meaning of the claim is not plain on its face. *Exxon Research & Eng'g Co.*, 265 F.3d at 1375. "If the meaning of the claim is discernable, even though the task may be formidable and the conclusion may be one over which

reasonable persons will disagree, [the Federal Circuit has] held the claim sufficiently clear to avoid invalidity on indefiniteness grounds." *Id.* Thus, only claims that are "insolubly ambiguous" even after the Court uses all tools at its disposal to try to construe the claims are invalid as indefinite. *See Source Search Techs., LLC*, 588 F.3d at 1076; *Star Scientific, Inc.*, 537 F.3d at 1371; *All Dental Prodx, LLC*, 309 F.3d at 780.

496. As this Court has already found, the claims of the patents-in-suit are amenable to construction. *Exxon Research & Eng'g Co.*, 265 F.3d at 1375; Claim Construction Order at 50-51. Throughout this case, the Court was presented with extensive evidence and has already rigorously analyzed whether the claim terms of the patents-in-suit are indefinite as a matter of law in the context of both claim construction and motions for summary judgment separately filed by both Defendants. No evidence was presented at trial that undermines the Court's claim construction decisions. To the contrary, the evidence presented at trial supports the Court's conclusion regarding the meaning of "average molecular weight" as used in the patent. (Sept. Tr. (Scandella) 1256:24-1257: 3; Sept. Tr. (Wall) 1828: 18-20; Sept. Tr. (Grant) 222:6-17; PTX 969 (Svec Dep.) at 9:19-23, 32:25-33:7, 34:18-22; PTX 962 (B. Rao 6/9/2010 Dep.) at 73:13-75:5, 116:3-13, 118:19-119:8; DTX 4022 (Varkony Dep.) 251:9-10, 251:12-18, 251:20-25, 252:3; PTX 964 (D. Rao Dep.) at 146:18-149:3, 174:17-178:13, 191:8-193:4; PTX 323 at MYL0001050-51, 58, 68-69, 73, 79-80, 84; PTX 281; PTX 741 at MYL0002927-932; PTX 349 at SDZ00017949; PTX 351 at SDZ00018608-11; PTX 986 at 26; PTX 317 at MYL0000110-11; PTX 959, 37:20-38:22; DTX 1701 at TEV001202496.)

(ii) Sandoz's "No Standards" Indefiniteness Argument Fails

497. According to Sandoz, without knowing the precise calibration standards used by Teva, and the manner in which the molecular weights of the standards was determined, a person of skill in the art would have been unable to determine whether a copolymer-1 sample meets the

claim limitations. This argument fails for at least the following reasons: First, there is no dispute that the level of skill in the art is high, and there is no evidence that such a highly skilled person would have been unable to accurately determine the molecular weight of a copolymer-1 sample. Second, the evidence at trial demonstrated that prior to the filing date of the patents-in-suit persons of skill would have understood from the scientific literature how to accurately determine the molecular weight of polydisperse polypeptide mixtures like copolymer-1. Dr. Grant testified regarding prior art texts and publications that explain how the molecular weight of polymers like copolymer-1 could be measured as of 1994. None of that prior art evidence was challenged. Third, Sandoz's reliance on the work done by Teva does not undermine this conclusion. As a matter of law, Teva's internal work is irrelevant to the analysis of whether the claims of the patent are definite. Moreover, even if relevant, Teva's experience shows that more than one type of standard (or method of measuring the molecular weights of standards) can be used to obtain accurate molecular weights for copolymer-1. (Sept. Tr. (Grant) 1452:1-13; DTX 3275; DTX 1701.) In fact, no evidence was presented at trial demonstrating that a person of skill was unable to accurately determine the "average molecular weight" of a copolymer-1 sample as that term has been interpreted by the Court based upon the disclosure of the patents-in-suit.

(1) Self-Standards Could Have Been Used to Determine the Molecular Weight of Copolymer-1

498. A person of ordinary skill in the art with the knowledge and experience described above could determine whether a copolymer-1 sample falls within the scope of the molecular weight limitations of the asserted claims using the information disclosed in the patents. It is undisputed that the specification specifically tells a person of ordinary skill to use size exclusion chromatography to determine the molecular weight of copolymer-1. (*See* PTX 1, at col. 3:6-8 (noting that molecular weight "was determined on a calibrated gel filtration column (Superose

12)".)

499. Defendants have not established by clear and convincing evidence that a person of ordinary skill in the art could not discern the boundaries of the claims as construed by the Court. *Power-One, Inc.*, 599 F.3d at 1350.

(a) Self-Standards Had Been Described in the SEC Literature by 1994

500. The evidence presented at trial demonstrated that size exclusion chromatography was a well-understood and well-described technique at the time the patent application was filed in 1994. (Sept. Tr. (Grant) 1421:4-24, 1400:16-21, 1401:9-11, 1414:8-1415:17, 1418:7-1421:3; PTX 514; PTX 566.) While calibration of the column was required, a person of ordinary skill could have used self-standards (either whole polymer or fractionated standards) to calibrate the SEC column. (Sept. Tr. (Grant) 1399:18-1400:13.) And while there were multiple "absolute" methods to measure the molecular weight of the self-standards, a person of ordinary skill would have known how to analyze that data to obtain a calibration curve that would result in an accurate molecular weight measurement by size exclusion chromatography. (Sept. Tr. (Grant) 327:9-16, 1403:3-13, 1421:4-24.) There is no need to describe such methods in the patent itself because, as shown through Dr. Grant's testimony, these techniques were well-known to the person of ordinary skill the art in 1994. (Sept. Tr. (Grant) 1421:4-24.) The law is clear—a patent applicant is not required to describe information in the patent specification that would be well-known to the person of skill in the art. *Koito Mfg. Co., Ltd.*, 381 F. 3d at 1156.

501. Because a person of ordinary skill could discern whether a copolymer-1 sample fell within the numerical molecular weight limitations of the asserted claims by using self-standards, the claims are not indefinite. *See Power-One, Inc.*, 599 F.3d at 1350; *Exxon Research & Eng'g Co.*, 265 F.3d at 1379.

(b) Teva Developed Self-Standards Without Significant Difficulty

502. Defendants spent a significant amount of time at trial offering evidence regarding a relatively few Teva internal research documents and documents generated by Teva's outside contractors. What Teva itself did, however, is irrelevant to the question of indefiniteness. *See* No. 08-cv-7611, D.I. 181, Memorandum and Order, September 7, 2010, at 3-4 (denying motion to strike expert declarations and noting that experts did not need information on what Teva actually did to render opinions on indefiniteness). A patent must provide a sufficient disclosure to allow a person of ordinary skill in the art to discern the metes and bounds of the claims, and determine whether an accused product falls within their scope, but there is no requirement that it provide a disclosure that allows replication of the patentee's underlying research. *Exxon Research & Eng'g Co.*, 265 F.3d at 1375; *Kinetic Concepts, Inc.*, 554 F.3d at 1022.

503. If what Teva did during its development were relevant to the question of definiteness, the evidence reinforces the conclusions that (1) self-standards could be used to measure the molecular weight of copolymer-1; and (2) the molecular weights of those self-standards could be measured using more than one absolute technique. The evidence shows that in its very first method for measuring the molecular weight of copolymer-1, Teva used self-standards to calibrate its SEC columns and determine the molecular weight of copolymer-1. (Sept. Tr. (Grant) 321:6- 324:11, 1450:15-18, 1451:23-25, 1452:1-3, 1462:18-23; Sept. Tr. (Scandella) 1307:22-1308:2; Sept. Tr. (Wall) 1828: 21-1829:5; DTX 3275.) By August 1987—over three months before Teva and Weizmann entered into a formal collaboration agreement on the development of copolymer-1—Teva had already developed a method for determining molecular weight of copolymer-1 using self-standards whose molecular weights had been determined by viscometry. (Sept. Tr. (Grant) 1452:4-13; DTX 1232; DTX 3275 at

TEV000304999-5000.) Haim Varkony, Teva's head of Chemistry, Manufacturing, and Controls (CMC) and Biological Development in Innovative R&D, testified that Teva developed its column calibration method in a matter of a few weeks. (DTX 4022 (Varkony Dep.) at 110:2-9.) He also testified that Teva had no difficulty in deciding to use SEC or in deciding to use copolymer-1 self-standards for calibration. (DTX 4022 (Varkony Dep.) at 252:18-22, 252:24.) Subsequently, Teva used the absolute measurement technique of multi-angle laser light scattering to measure the molecular weights of its self-standards. (DTX 1701; DTX 4022 (Varkony Dep.) at 58:4-6.)

(2) Universal Calibration Was Known in 1994 and Would have Provided Accurate Molecular Weights for Copolymer-1

504. In addition to self-standards, the record at trial also demonstrated that universal calibration was available to a person of skill in the art in 1994 and that such persons could have used that technique to accurately determine the molecular weight of copolymer-1. Using this method, a person of ordinary skill could discern the scope of the claims and whether a particular copolymer-1 batch met the limitations of those claims, and hence the claims are not indefinite. *See Power-One, Inc.*, 599 F.3d at 1350; *Exxon Research & Eng'g Co.*, 265 F.3d at 1379.

505. Universal calibration was first described in the late 1960s, and by 1994, there was extensive literature on universal calibration and a large number of studies that showed that this technique worked quite well for different types of polymers. (PTX 970 (Svec Dep.) at 296:16-22, Sept. Tr. (Grant) 1401:12-18; PTX 514 at 213-17; PTX 553 at 73-76.) Dr. Grant testified that in 1994, a person of skill in the art could have used universal calibration to accurately determine the peak average molecular weight and the molecular weight distribution of a copolymer-1 sample or a sample of TFA copolymer-1 without undue experimentation. (Sept. Tr. (Grant) 1430:8-1432:11; PTX 970 at 382:8-382:13; 384:23-385:6: 385:8-385:19.) It is

unrebutted that universal calibration was known to persons skilled in the art in 1994, and that it could readily be used to accurately determine the average molecular weight and the molecular weight distribution of a sample of copolymer-1.

506. In sum, Defendants have failed to carry their burden of proving by clear and convincing evidence that the claims are indefinite. The Court has already construed "average molecular weight," and the evidence adduced at trial shows that persons of skill in the art in 1994 would have understood how to accurately measure the "average molecular weight" of copolymer-1 using either self-standards or universal calibration, both of which were well-known methods. A person of ordinary skill in the art, based upon the disclosures in the patent and her own knowledge, could thus discern the scope of the claims. The claims of the patents-in-suit are definite. *See Power-One. Inc.*, 599 F.3d at 1350; *Exxon Research & Eng'g Co.*, 265 F.3d at 1379.

E. Conclusions of Law Concerning Enablement

507. Out of the same set of assertions used to support its indefiniteness theory, Sandoz fashions an argument that the asserted claims likewise do not satisfy the enablement requirement of 35 U.S.C. § 112.[6] Section 112 requires a patent specification to provide a description of the invention "as to enable any person skilled in the art to which it pertains . . . to make and use [the invention]." 35 U.S.C. § 112.

[6] Sandoz asserts that the claims of the patents-in-suit are not enabled while at the same time Mylan argues that those same claims would have been obvious over the prior art. A tension exists between Mylan's argument that, on the one hand, it would have been obvious for a person of skill in the art to make the claimed invention on the basis of the teachings of the prior art, and Sandoz's argument that, on the other hand, the patent specification itself does not provide sufficient information to make and use the claimed invention. *Hybritech, Inc.*, 802 F.2d at 1384 (Fed. Cir. 1986). This tension undermines both arguments.
(continued…)

508. As discussed above in ¶¶ 438-443, in determining whether a claim is enabled, courts have looked the seven *Wands* factors set forth in *In re Wands*, 858 F.3d at 737.

509. Here, Defendants have failed to carry their burden of proving by clear and convincing evidence that the asserted claims are invalid for lack of enablement. There was no evidence presented at trial demonstrating that a person of skill in the art would have been unable to make and use a lower molecular weight copolymer-1 as claimed in the patents-in-suit. To the contrary, the evidence presented at trial demonstrated that the highly skilled person of skill in the art of the patents-in-suit had at their disposal the information necessary to make the claimed lower molecular weight copolymer-1 and measure its molecular weight to determine whether it met the claim limitations without undue experimentation.

(i) The Level of Skill In the Art of the Patents-In-Suit Is High

510. Looking first at *Wands* factor 6, the parties and the experts unanimously agree that the level of skill in the art of the patents-in-suit is high. (*See* Sept. Tr. (Grant) 189:22-190:6; Sept. Tr. (Scandella) 1190:15-20, 1300:20-1301:9; Sept. Tr. (Zeiger) 809:10-811:15; PTX 806 at 3; PTX 4030 at 4.) Defendants face the burden, therefore, of proving by clear and convincing evidence that such a highly-skilled scientist would not have been able to make and use the claimed lower molecular weight copolymer-1. *In re Wands*, 858 F.2d at 740 (weighing the high level of skill in the art in holding that undue experimentation would not be required).

(ii) The Prior Art and the Patent Provide Predictable Guidance to Measuring Molecular Weight Using Size Exclusion Chromatography

511. Turning next to *Wands* factors 2, 5, and 7, the trial evidence also showed that the

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The opposite is not true, however. The invention was not obvious but *with the benefit of the disclosures in the specification and the claims* a person of ordinary skill in the art with only routine experimentation would understand the claimed inventions and be able to practice them.

highly skilled person of skill in the art would have had access to a large body of scientific literature, published over the course of many years, describing how to carry out SEC on polydisperse polymers like copolymer-1. The patents specifically direct a person of skill to use size exclusion chromatography, and the prior art gave significant direction and guidance to the person of skill in the art on that technique. (PTX 566; Sept. Tr. (Grant) 1410:10-1412:5, 1414:8-21, 1418:19-1419:21; PTX 553 at 70.) As discussed above, a person of ordinary skill could have calibrated an SEC column, to obtain an accurate molecular weight for copolymer-1, using either self-standards or universal calibration. Moreover, there was no evidence presented at trial that the science involved in the molecular weight determination of copolymer-1 is poorly understood or unpredictable or that the determination of the molecular weight of copolymer-1 using SEC would have presented any significant problems for the person of skill in the art.

512. Thus, the trial evidence showed that the person of skill would have addressed the molecular weight issue armed with an extensive and well-developed body of scientific literature addressing SEC. The literature provided significant guidance with respect to both self-standards and universal calibration. There was, moreover, no evidence that the molecular weight determination of copolymer-1 poses any particular or unusual difficulties. In such situations, there is no need for a patent specification to provide extensive discussion of a technique that was well-known and thoroughly described in the prior art. *Hybritech Inc.*, 802 F.2d at 1384 ("[A] patent need not teach, and preferably omits, what is well known in the art."); *see also Monsanto Co.*, 459 F.3d at 1338; *Telectronics, Inc.*, 857 F.2d at 785. The patent specification's reference to a calibrated gel filtration column would be sufficient guidance for a person of skill in the art to accurately determine the average molecular weight and molecular weight distribution of a copolymer-1 sample in view of the teaching and guidance provided by the prior

art.

(iii) The Quantity of Experimentation is Not Undue

513. The first *Wands* factor similarly supports the conclusion that the claims of the patents-in-suit are enabled. Dr. Grant testified at trial that a person of skill in the art could have accurately determined the average molecular weight or molecular weight distribution of a copolymer-1 sample based on the patent disclosure without undue experimentation. (Sept. Tr. (Grant) 1422:9-14.) Dr. Grant's testimony was based on the teachings of the patents-in-suit in view of the guidance provided by the prior art scientific literature on on SEC generally and on both self-standards and universal calibration. (Sept. Tr. (Grant) 1422:9-14.)

514. Sandoz offered the testimony of Dr. Scandella, who testified that the use of self-standards would be a major research project (Sept. Tr. (Scandella) 1251:13-1252:9), and Dr. Wall, who testified that a person of skill in the art would give up trying to determine the molecular weight of copolymer-1 after attempting to use globular protein standards. (Sept. Tr. (Wall) 1767:10-1770:22.)

515. Dr. Wall admitted that he personally stopped using SEC after 1965 and that he has never used SEC to determine average molecular weights of a mixture of polypeptides such as copolymer-1. (Sept. Tr. (Wall) 1758:21-1759:10, 1759:20-1760:13.) Moreover, Dr. Wall does not have any publications that describe the use of SEC to measure the molecular weight of a polydispersed mixture of polypeptides. (Sept. Tr. (Wall) 1758:4-12.) In fact, despite having testified as an expert in several litigations, Dr. Wall has never been proffered as an expert in SEC. (Sept. Tr. (Wall) 1760:14-17.)

516. There is no evidence to support these opinions offered by Drs. Scandella and Wall, but even if significant experimentation were required that would not mandate the conclusion that the amount of experimentation was "undue." *Falko-Gunter Falkner*, 448 F.3d at

1365 (finding claims to a vaccine were enabled, where the skill level in the art was high, and agreeing with the BPAI that "the mere fact that the experimentation may have been difficult and time consuming does not mandate a conclusion that such experimentation would have been considered 'undue' in this art").

517. Moreover, the only evidence that Defendants' experts rely on in support of these opinions are documents showing Teva's early work on its copolymer-1 product. Evidence of what Teva's scientists did to develop and submit a commercial product to the FDA in the late 1980s and throughout the 1990s is not probative of what a person of skill in the art of the patents-in-suit would have done or understood in 1994 unless Defendants affirmatively establish that the scientists working at Teva were, in fact, people of ordinary skill in the art of SEC. *Johns Hopkins Univ.*, 152 F.3d at 1360 (holding that evidence of efforts of inventor's laboratory was insufficient as a matter of law because of failure to show that persons working in laboratory were of ordinary skill in the art). Defendants offered no evidence that the scientists working at Teva had the experience in SEC of a "persons of ordinary skill in the art," as defined by the experts in this case.[7]

518. The only evidence of record identified by Defendants' experts suggests that there were no people with the requisite training and experience in SEC of a "person of ordinary skill in the art" working at Teva at the time of the work relied on by Defendants. There is likewise no evidence that the Teva employees working to measure the molecular weight of copolymer-1 at the beginning of the project were familiar with all of the prior art. Defendants identified issues with Teva's development beginning in 1987. When asked, the only person that Sandoz's' expert

[7] Defendants have similarly offered no evidence demonstrating that a person of skill in the art *having in hand the teachings of the patents-in-suit* would have been unable to make and used the claimed invention without undue experimentation.

Dr. Scandella could point to as potentially being a person of skill in the art of SEC was Dr. Alexander Gad, but the evidence of record shows that Dr. Gad did not start working at Teva until 1989 (Sept. Tr. (Scandella) 1301:10-25; DTX 4016 (Gad Dep. Nov. 10, 2009) at 12:10-13), two years after Teva developed its molecular weight determination method using self-standards. (Sept. Tr. (Grant) 321:6-322:3, 322:9-324:11; DTX 3275 at TEV000304995; Sept. Tr. (Grant) 324:12-325:13, 1450:15-18, 1451:23-25, 1452:1-13; Sept. Tr. (Scandella) 1307:22-1308:2; Sept. Tr. (Wall) 1828:21-1829:5; DTX 1762 at TEV003017831.) Thus, the Teva work relied on by Defendants is irrelevant to the question of enablement as a matter of law. *See e.g.*, *Johns Hopkins Univ*, 152 F.3d at 1360.

519. Even assuming that evidence of Teva's work on copolymer-1 were relevant to the issue of enablement, Defendants have misinterpreted the evidence. The evidence presented at trial shows that the first copolymer-1 SEC molecular weight determination method developed at Teva in 1987 utilized copolymer-1 self-standards, and that the development took only a matter of weeks. (DTX 4022 (Varkony Dep.) at 110:2-9.) The evidence also shows that Teva continued to use self-standards to measure the molecular weight of copolymer-1 from 1987 through the filing of the NDA in 1995 and approval of the NDA for Copaxone® in 1996. (Sept. Tr. (Grant) 1462:24-1463:4; Sept. Tr. (Wall) 1829:6-9.) None of the documents relied on by Defendants' experts demonstrate that Teva had any difficulty developing a method to measure the molecular weight of copolymer-1 using SEC. To the contrary, to the extent that evidence of Teva's work is relevant to the enablement issue, it demonstrates that the use of SEC to determine the peak molecular weight of copolymer-1 was a relatively straightforward process and supports a determination that the claims are enabled. *In re Wands*, 858 F.2d at 739-740 (finding no undue experimentation after analyzing initial efforts of inventor).

(iv) The Patents Contain Working Examples

520. Turning to the third *Wands* factor, the patents-in-suit contain working examples. First, Example 1 of the patent discloses the use of SEC to determine the average molecular weight of copolymer-1 samples. (PTX 1, col. 2:51–3:18.) The example discloses that the molecular distribution of the copolymer-1 samples was determined using a calibrated size exclusion chromatography column. (PTX 1, col. 3:9-18.)

521. Momenta has acknowledged that if one were to follow of the disclosure of patents-in-suit, the resulting compound would be copolymer-1. Specifically, Dr. Mani Iyer, who developed the Momenta process, acknowledged that the process for making copolymer-1 used by Momenta tracks the steps disclosed and claimed in claim 1 of the '808 patent and results in copolymer-1 with an average molecular weight of 5-9 kilodaltons. (PTX 960 (Iyer Dep.) at 146:12-151:22.) Mylan's expert Dr. Hurwitz also testified that the methods described in the patents would enable a person of ordinary skill in the art to make a batch of copolymer-1. (PTX 959 (Hurwitz Dep.) at 130:15-20.) Thus, the working examples found in the patents-in-suit support a finding of enablement. *See e.g.*, *In re Wands*, 858 F.2d at 740 (finding no undue experimentation, where disclosure presents working examples).

(v) The Nature of the Invention and Breadth of the Claims

522. Finally, the patents-in-suit are directed to a lower molecular weight form of copolymer-1 for the treatment of multiple sclerosis. High molecular weight copolymer-1 was known in the prior art and the concepts of molecular weight and the measurement of molecular weight using size exclusion chromatography were well-known in 1994. As discussed above, there was a significant quantity of scientific literature describing SEC and its use for determining the molecular weight of polydisperse polymers such as copolymer-1. There is nothing about the nature of the invention claimed in the patents-in-suit that supports a finding that the claims are

not enabled.

523. Based upon a review of the evidence presented at trial, and a consideration of the *Wands* factors, there is no evidence that the claims of the patents-in-suit are overbroad, or that the breadth of the claims supports a finding of nonenablement. A person of skill would understand the meaning and scope of the claims of the patents-in-suit and was able to properly construe each of the disputed claim terms. (Claim Construction Order at 3.)

524. In sum, Defendants have failed to show that application of *any* of the *Wands* factors leads to a conclusion of lack of enablement. To the contrary, the evidence presented at trial demonstrates that a person of skill in the art would have been able to make and measure the molecular weight of copolymer-1 without undue experimentation.

VIII. FINDINGS OF FACT AND CONCLUSIONS OF LAW RELATING TO MYLAN'S BEST MODE DEFENSE

525. Mylan, but not Sandoz, argues that the patents-in-suit are invalid for violating the best mode requirement of 35 U.S.C. § 112 because inventor Eliezer Konfino failed to disclose: (a) the use of phenol as a bromine scavenger in the claimed synthetic process; and (b) copolymer-1 with "low bromotyrosine" amounts. As set forth below, both of these arguments fail.

526. Mylan's first best mode argument, that inventor Eliezer Konfino failed to disclose a preference for using phenol as a bromine scavenger for HBr/acetic acid as part of his claimed synthetic process, applies only to claims with limitations involving the use of HBr/acetic acid as part of a process—claim 1 of the '808 Patent, '589 Patent, '476 Patent, and '161 Patent, and claims 1-3 of the '898 Patent and '430 Patent. This argument thus does not apply to product or method of treatment claims that do not recite process limitations (*see* claims 1, 8-10, 12, 23, 30, and 31 of the '539 patent; claims 1 and 8 of the '098 Patent) or to process claims that do not

contain a limitation concerning the use of HBr/acetic acid (*see* claims 1 and 6 of the '847 patent).

A. Legal Principles

527. When challenging the validity of patent claims for failure to disclose the best mode of practicing the invention, an alleged infringer bears the burden to prove a best mode violation by clear and convincing evidence. *ALLVoice Computing PLC v. Nuance Comm'n, Inc.*, 504 F.3d 1236, 1240 (Fed. Cir. 2007); *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1330 (Fed. Cir. 2002). The test for whether a best mode exists involves a two-prong factual inquiry. *In re Omeprazole Patent Litig.*, 490 F. Supp. 2d at 501-502.

528. The first prong is subjective. The inquiry is whether the inventor considered a particular mode of practicing the invention to be superior to all other modes at the time the patent application was filed. *Id.* If the inventor had no subjective preference for one mode over all others as of the filing date of the application, then the inquiry ends and there cannot be a failure to comply with the best mode requirement. *See, e.g.*, *High Concrete Structures, Inc. v. New Enter. Stone & Lime Co., Inc.*, 377 F.3d 1379, 1382 (Fed. Cir. 2004); *Young Dental Mfg. Co. v. Q3 Special Prods., Inc.*, 112 F.3d 1137, 1144 (Fed. Cir. 1997). This is a highly subjective inquiry, focusing only on the inventor's state of mind. *See Engel Indus., Inc. v. Lockformer Co.*, 946 F.2d 1528, 1533 (Fed. Cir. 1991).

529. If a defendant proves that the inventor had a best mode, the second prong requires clear and convincing proof that the inventor failed adequately to disclose that best mode. *In re Omeprazole Patent Litig.*, 490 F. Supp. 2d at 502.

530. The contours of the best mode requirement "are defined by the claimed invention." *N. Telecom Ltd. v. Samsung Elecs. Co., Ltd.*, 215 F.3d 1281, 1286 (Fed. Cir. 2000); *see also Teleflex, Inc.*, 299 F.3d at 1329-30 ("[A]nalysis of compliance with the best mode requirement must begin and remain focused on the language of the claim."). Thus, the first step

in the best mode analysis is to define the scope of the claims. *N. Telecom Ltd.*, 215 F.3d. at 1287. Unclaimed subject matter is not subject to the best mode requirement. *Engel Indus., Inc.*, 946 F.2d at 1531. Best mode is assessed from the date of the filing of the parent application and inventors are under no obligation to update the best mode disclosed in an application when subsequent continuations are filed. *Id.* at 1534; *see also Transco Prods. Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 557 (Fed. Cir. 1994).

531. Even if one demonstrates that certain aspects of an inventor's best mode are not disclosed in a patent, there is no violation of the statutory requirement if those undisclosed aspects are "production details." *Young Dental Mfg. Co.*, 112 F.3d at 1144; *see also Liquid Dynamics Corp. v. Vaughan Co., Inc.*, 449 F.3d 1209, 1223 (Fed. Cir. 2006); *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 963 (Fed. Cir. 2001). The Federal Circuit has explained that there are at least two types of production details that need not be disclosed to satisfy the best mode requirement. First are "true" production details or commercial considerations that do not relate to the quality or nature of the invention, such as "equipment on hand or prior relationships with suppliers." *Young Dental Mfg. Co.*, 112 F.3d at 1144. Second are "routine details" that would be "apparent to one of ordinary skill in the art." *See id.* (citing *Engel Indus., Inc.*, 946 F.2d at 1532).

B. Findings of Fact

(i) The Use of Phenol to Pretreat HBr/Acetic Acid

532. The only inventor named on the patents-in-suit involved in the development of the claimed synthetic process, used to consistently and reproducibly produce a lower molecular weight copolymer-1, was Eliezer Konfino. (July Tr. (Pinchasi) 66:16-68:25; PTX 1 at 4:29-6:3; DTX 3567 (Konfino Dep. Tr.) at 60:8-63:9, 182:9-19, 184:6-11; DTX 4019 (Pinchasi 12/21/2009 Dep.) at 20:3-21:11.)

533. Mr. Konfino was a bench chemist who was involved in development activity but was not involved in manufacturing copolymer-1 on a commercial scale. (Sept Tr. (Kent) 761:20-23, 1736:22-25; DTX 3567 (Konfino Dep.) at 25:8-23, 28:18-24; DTX 4019 (Pinchasi 12/21/2009 Dep.) at 18:6-18, 20:3-11.) Mr. Konfino retired and ceased all involvement with copolymer-1 development in 1991. (PTX 3567 (Konfino Dep.) at 29:14-19, 34:11-14, 39:2-5, 117:2-15.)

534. In some experiments, Mr. Konfino used a reagent called phenol to pre-treat the HBr/acetic acid he used during the debenzylation step of the synthetic process he was developing. (DTX 3567 (Konfino Dep.) at 113:17-114:21.) During these experiments, Mr. Konfino was using phenol to reduce or "scavenge" free bromine from the HBr/acetic acid he was using as part of the debenzylation reaction. (DTX 3567 (Konfino Dep.) at 113:17-114:5.)

535. Free bromine present in HBr/acetic acid can react with tyrosine moieties to form an impurity known as bromotyrosine. (Sept. Tr. (Gokel) 1597:24-1600:23; Sept Tr. (Owens) 631:21-632:6; Sept. Tr. (Kent) 771:19-23.) Reducing the presence of free bromine, therefore, can reduce amounts of bromotyrosine in copolymer-1. (Sept. Tr. (Owens) 611:15-25; Sept. Tr. (Kent) 666:16-24.)

536. At the time Mr. Konfino was developing his synthetic process, Teva's specification for bromotyrosine content in copolymer-1 was less than 0.5%. (Sept. Tr. (Kent) 1736:15-17; PTX 52 at TEV1177354-357; DTX 1270 at 211.)

537. In many other experiments, however, Mr. Konfino did not use phenol to scavenge free bromine. (Sept. Tr. (Kent) 761:20-762:2, 762:23-765:25, 1737:1-4; PTX 52 at TEV1177220, TEV1177226-227, TEV1177352-533, TEV1177354.) Indeed, in experiments conducted in March 1991—the last month for which his lab notebooks report copolymer-1

experiments before his retirement—Mr. Konfino used HBr/acetic acid from the same supplier, once with phenol and once without phenol and in each case obtained copolymer-1 with bromotyrosine amounts that were within Teva's specification at that time – less than 0.5%. (Sept. Tr. (Kent) 763:25-765:25; PTX 52 at TEV1177354-357.) Mr. Konfino obtained copolymer-1 and TFA copolymer-1 with a bromotyrosine content of less than 0.5% in a number of other experiments in which he did not use phenol. (Sept. Tr. (Kent) 761:24-762:2, 762:23-765:25, 1737:1-4; PTX 52 at TEV1177220, TEV1177226-227, TEV1177352-533, TEV1177354.) Mr. Konfino continued to make copolymer-1 without using phenol until he left Teva in 1991. (Sept. Tr. (Kent) 762:3-11.)

538. Mr. Konfino never considered the use of phenol to be part of the synthetic process that he developed. (DTX 3567 (Konfino Dep.) at 113:22-117:15.) He testified at his deposition as follows:

> Q. So you were using phenol to clean hydrobromic acid?
> A. I made a lot of experiments that did not become part of the process, and that's one of them.
> * * *
> Q. Did you use bromine scavengers in your Copolymer-1 processes?
> A. Not in my process.
> Q. In your process, did you want to get rid of excess bromine?
> A. There was no need to
> Q. Why?
> A. We changed solvents or we changed other conditions, so there was no need.
> * * *
> Q. What do you consider to be your process?
> A. The process is written down, is described in the patent.
> * * *
> Q. What differences, if any, are there between the process described in your patent and the process for making Copolymer-1?
> A. I believe there is no difference at all
> * * *
> Q. I'm asking whether you learned more things about the Copolymer-1 process at Teva between your departure in 1991 and your signing of the patent application in 1994?

A. The 1994 patent described my process.
Q. And that was your process as of 1991?
A. The same.

(PTX 3567 (Konfino Dep.) at 113:23-117:15.)

539. Documents cited by Mylan at trial do not support a conclusion that Mr. Konfino considered the use of phenol to be part of "his process" or a "best" way to make copolymer-1. Mylan's expert on best mode issues, Dr. Kent, cited to a document authored by Mr. Konfino, stating that pretreating HBr/acetic acid "with 1% phenol proved to be the most convenient" way to lower the bromotyrosine level of copolymer-1. (PTX 708-T at TEV000324554.) But it is not reasonable to infer that Mr. Konfino viewed the use of phenol to be part of his process simply because he described it as "convenient"—particularly in view of his testimony in which he explained that other means of controlling free bromine were available to him. (Sept. Tr. (Kent) 765:17-23; PTX 3567 (Konfino Dep.) at 113:22-117:15.) As Dr. Kent put it, phenol could have been "convenient" because it was simply "the nearest [bottle] when [Mr. Konfino] put his hand out to the lab bench." (Sept. Tr. (Kent) 771:13-16.) Another possible, reasonable inference is that phenol was convenient simply because it was the least expensive way to pretreat HBr/acetic acid. The mere characterization of phenol as a "convenient" means of reducing free bromine does not provide clear and convincing evidence that it was Mr. Konfino's best way to make copolymer-1.

540. Mylan also cites to a manufacturing protocol for copolymer-1 as evidence of Dr. Konfino's best mode. (DTX 999 at TEV001222365-RC—387-RC.) This document is irrelevant to Mr. Konfino's subjective state of mind, however. His name appears nowhere in the document. (Sept. Tr. (Kent) 765:24-766:8; DTX 999 at TEV001222365-RC—387-RC.) And it is undisputed that Mr. Konfino was a bench scientist who was not involved in manufacturing copolymer-1 on a commercial scale. (Sept. Tr. (Kent) 1736:22-25; DTX 3567 (Konfino Dep.) at

25:8-23, 28:18-24; DTX 4019 (Pinchasi 12/21/2009 Dep.) at 18:6-18, 20:3-11.)

541. Lastly, Mylan cites to a 1993 report listing several "major improvements" to the manufacturing process of copolymer-1, one of which reads: "HBr/acetic acid is treated with phenol before use, thus preventing side reaction of free residual bromine with a tyrosine moiety." (DTX 1270 at TEV000312175.) Again, this document does not list Mr. Konfino as an author and was written in 1993, more than one year after Mr. Konfino retired and ceased all involvement in the Copaxone® project. (Sept. Tr. (Kent) 766:18-767:5; DTX 1270.) Thus, this document cannot possibly reflect Mr. Konfino's subjective state of mind at the relevant time – 1991.

542. It is also undisputed that the use of phenol would have been a routine production detail at the time of the patent application. Phenol was readily available in 1994 and was "widely used in peptide chemistry." (Sept. Tr. (Kent) 771:9-16.) It was well known to persons of skill at the relevant time that some amount of free bromine could be present in HBr/acetic acid depending on the quality or type of HBr/acetic acid used. (Sept. Tr. (Gokel) 1592:14-1593:4; Sept. Tr. (Kent) 754:7-10.) It was also well known at the time that phenol could be used to reduce the presence of free bromine in HBr/acetic acid. (Sept. Tr. (Gokel) 1591:11-1592:13; Sept. Tr. (Kent) 756:5-8; PTX 961 (Kota Dep.) at 130:18-131:18.) Using phenol to reduce the presence of free bromine in HBr/acetic acid thus would have been a routine production detail at the time of the patent application. (Sept. Tr. (Gokel) 1591:11-1592:13; Sept. Tr. (Kent) 756:5-8; PTX 961 (Kota Dep.) at 130:18-131:18.)

(ii) The Level of Bromotyrosine Impurity

543. There is no evidence that Mr. Konfino viewed any particular level of bromotyrosine copolymer-1 to be part of his invention. Mylan offered no testimony from Mr. Konfino on this question and the only available evidence indicates that bromotyrosine was not a

major concern to Mr. Konfino. In an internal Teva report authored by Mr. Konfino, it was noted that bromotyrosine had been studied and determined to be "non-toxic." (PTX 708 at TEV000324554.) Dr. Kent confirmed that Mr. Konfino had found bromotyrosine to be non-toxic and offered no opinion on the effect of bromotyrosine on the safety or efficacy of copolymer-1. (Sept. Tr. (Kent) 668:22-669:10, 774:8-24.) Indeed, Dr. Kent admitted he didn't possess the expertise necessary to assess the question. (Sept. Tr. (Kent) at 774:14-19.) Dr. Owens also described the impact of bromotyrosine upon the safety or efficacy of copolymer-1 as an "unknown." (Sept. Tr. (Owens) 633:13-16.)

544. There also is no evidence that Mr. Konfino attempted to make a "low bromotyrosine copolymer-1" during his time at Teva. Mylan's expert, Dr. Kent defined "low bromotyrosine copolymer-1" to be a product that complied with Teva's 1995 NDA specification for bromotyrosine, which was less than 0.2%. (Sept. Tr. (Kent)1731:9-1732:3.) At the time Mr. Konfino was at Teva, however, the specification for bromotyrosine was 0.5%. (Sept. Trial Tr. (Kent) 1736:15-17; PTX 52 at TEV1177354-357; DTX 1270 at 211.) Thus, there is no support for a finding that Mr. Konfino subjectively viewed "low bromotyrosine" levels as a requirement for the copolymer-1 he was making.

545. The evidence also supports a finding that reducing amounts of bromotyrosine was, again, a routine production detail. Bromotyrosine is an impurity that may be created during the synthetic process used to make copolymer-1. (Sept. Tr. (Gokel) 1603:13-1604:2; Sept. Tr. (Owens) 615:8-16, 634:22-635:8; PTX 349 at SDZ00017963.) All of the experts and parties agreed that bromotyrosine is an impurity in the context of copolymer-1. (Sept. Tr. (Gokel) 1597:24-1600:23, 1603:13-1604:2, 1606:17-1607:18; Sept. Tr. (Kent) 771:19-772:10; Sept. Tr. (Owens) 632:4-633:12; PTX 963 (B. Rao 6/30/2010 Dep.) at 240:7-9; PTX 320 at

MYL0000685-686; PTX 349 at SDZ0017963; PTX 78 at TEV000000196.) Bromotyrosine is one of a long list of impurities that are controlled in copolymer-1. (Sept. Tr. (Gokel) 1597:24-1600:23; PTX 78 at TEV000000196-197; PTX 320 at MYL0000685-686.)

546. There also is no disagreement that it is standard practice within the pharmaceutical industry to reduce impurities in a product. Mylan's expert, Dr. Kent, and fact witness, Dr. Owens, both agreed that reducing impurities like bromotyrosine is standard practice in the pharmaceutical industry. (Sept. Tr. (Kent) 773:3-14; Sept. Tr. (Owens) 633:7-12.) This is consistent with the testimony of Teva's expert, Dr. Gokel, who explained that it would be a "routine matter for anyone trying to make a product at any scale, laboratory, or manufacturing, to try to reduce impurities as much as possible." (Sept. Tr. (Gokel) 1597:18-23; 1607:19-1608:2.)

547. Furthermore, there is no evidence suggesting that the presence of bromotyrosine has any impact upon the quality or nature of copolymer-1. (Sept. Tr. (Kent) 774:8-24; Sept. Tr. (Owens) 633:13-24.) Indeed, the record supports a finding that bromotyrosine has no impact upon the quality or nature of copolymer-1, since, as explained above, it was determined to be "non-toxic." (Sept. Tr. (Kent) 668:22-669:10; PTX 708 at TEV000324554.)

548. Mylan cites to U.S. Patent No. 7,495,072, issued in 2009 to inventor Ben Zion Dolitzky and assigned to Teva, as evidence that using phenol to reduce bromotyrosine was not routine. (DTX 1925.) The '072 patent, however, does not support such a finding.

549. The '072 patent is directed to a solution for a manufacturing problem that arose many years after Mr. Konfino left Teva in 1991. (Sept. Tr. (Gokel) 1595:9-15, 1596:23-1597:14.) Specifically, the '072 patent discusses means of using bromine scavengers, including phenol, to *eliminate* the presence of bromotyrosine and to remove a red color that had been detected in syringes of aqueous solutions of Copaxone®. (Sept. Tr. (Gokel) 1593:8-1594:2,

1594:18-1595:20; DTX 1925 at col. 10: 5-10, col. 12:41-col.13:67.) The patent explicitly states that older methods of Copaxone® production—which are not claimed in the '072 patent— used phenol as a bromine scavenger to produce copolymer-1 with reduced levels of bromotyrosine. (Sept. Tr. (Gokel) 1631:7-1633:17; DTX 1925 at col. 12:41-13:67.) The '072 patent, therefore, is directed to a "new" and improved process that produces Copaxone® with no detectable amounts of bromotyrosine and no red color. (Sept. Tr. (Gokel) 1631:7-1632:21; DTX 1925 at col. 12:41-13:67.)

550. Dr. Kent admitted that the bromotyrosine specification in the '072 patent (0.2% or none detectible) is lower than the specification in place when Mr. Konfino was working at Teva (0.5%), providing further evidence that the '072 patent was directed to a different problem and is irrelevant to Mr. Konfino's experiments. (Sept. Tr. (Kent) 1735:1-1736:17.)

551. The '072 patent is thus irrelevant to the question of whether using phenol as a bromine scavenger was a routine detail in 1994. Since this patent is directed to a different problem, namely the *elimination* of bromotyrosine and the removal of an unwanted color from an aqueous form of Copaxone® rather than merely *reducing* bromotyrosine, it does not establish that using phenol to reduce amounts of free bromine was not routine as of 1994.

C. Conclusions of Law

(i) The Patents' Lack of Disclosure Regarding Phenol is Not a Best Mode Violation

552. There is no dispute that the patents-in-suit do not disclose the use of phenol to pretreat HBr/acetic acid used in the debenzylation step of the synthetic process claimed in the patents-in-suit. Defendants have failed, however, to prove clearly and convincingly that this amounts to a best mode violation.

553. Mr. Konfino testified unequivocally that the use of phenol was not part of "his

process" at the time he retired from Teva in 1991 and the process he used is the one described in the patents-in-suit. (PTX 3567 (Konfino Dep.) at 113:22-117:15.) This unambiguous and unchallenged testimony is strong evidence that Mr. Konfino did not subjectively consider the use of phenol part of his best mode of making copolymer-1. *Minco, Inc. v. Combustion Eng'g, Inc.*, 95 F.3d 1109, 1116 (Fed. Cir. 1996) (affirming finding of no best mode where trial court relied only on inventor's testimony that the undisclosed information was a production decision and inventor did not consider it to be a superior method of operation); *Shearing v. Iolab Corp.*, 975 F.2d 1541, 1546 (Fed. Cir. 1992) (affirming jury verdict of no best mode violation where inventor testified that, although he sometimes used alleged best mode to align lens, he had no preference and embraced any method that did so).

554. The documents relied upon by Mylan at trial reinforce this conclusion. Mr. Konfino's lab notebooks reveal that he only used phenol in some of his experiments synthesizing copolymer-1, made copolymer-1 without using phenol a number of times and was still making copolymer-1 without using phenol at the time he left Teva in 1991. The other documents relied upon by Mylan are either irrelevant to Mr. Konfino's subjective state of mind or do not support a conclusion that Mr. Konfino viewed use of phenol to be part of a best way of making copolymer-1. Mylan has thus failed to demonstrate that Mr. Konfino subjectively viewed the use of phenol to be part of a best mode. *See Minco, Inc.*, 95 F.3d at 1116; *Shearing*, 975 F.2d at 1546; *In re Omeprazole Patent Litig.*, 490 F. Supp. 2d at 503-504.

555. Having failed to meet this requisite first prong, Mylan's best mode defense fails. *See High Concrete Structures, Inc.*, 377 F.3d at 1382; *Young Dental Mfg. Co.*, 112 F.3d at 1144. Even if an examination of the second prong of the defense was necessary, however, Mylan has also failed to demonstrate that the disclosure of phenol would have been required in order to

satisfy the best mode requirement. Since phenol was both widely used in peptide chemistry at the time of the patent application and was a known scavenger of free bromine, its use was both a "true" and "routine" manufacturing detail that need not be disclosed in the patents to comply with the best mode requirement. *See, e.g.*, *Young Dental Mfg. Co.*, 112 F.3d at 1144.

(ii) The Patents' Lack of Disclosure Regarding a "Low Bromotyrosine" Content of Copolymer-1 Also is Not a Best Mode Violation.

556. Mylan's other best mode argument—that the patents should have disclosed a "low bromotyrosine" content for copolymer-1—also fails because Mylan has failed to satisfy both prongs of the best mode defense. Mylan offered no direct evidence from Mr. Konfino supportive of this claim. Indeed, Mr. Konfino was never questioned about the bromotyrosine content of copolymer-1 during his deposition. (PTX 3567 (Konfino Dep.).) The only evidence offered at trial from which any inference concerning Mr. Konfino's subjective beliefs could be drawn suggests that bromotyrosine was not important to him. In 1991, Mr. Konfino reported that bromotyrosine was not toxic and Dr. Kent acknowledged this was the case at trial. (Sept. Tr. (Kent) 668:22-669:10; PTX 708 at TEV000324554.) Mylan again has failed to satisfy the subjective prong of the best mode defense here. *See Minco, Inc.*, 95 F.3d at 1116; *Shearing*, 975 F.2d at 1546; *In re Omeprazole Patent Litig.*, 490 F. Supp. 2d at 503-504.

557. Producing a copolymer-1 with lower bromotyrosine levels also amounts to a "true" and "routine" manufacturing detail that need not be disclosed to comply with the best mode requirement. The evidence demonstrates that bromotyrosine is an impurity in copolymer-1 and it is standard practice in the pharmaceutical industry to reduce the amounts of impurities in a pharmaceutical product like copolymer-1. (Sept. Tr. (Kent) 773:3-14; Sept. Tr. (Owens) 633:7-12; Sept. Tr. (Gokel) 1597:18-23.) Mylan also failed to offer any evidence that the presence of bromotyrosine has any impact upon the "quality or nature" of copolymer-1. (Sept. Tr. (Kent)

774:8-24; Sept. Tr. (Owens) 633:13-16.) For the reasons set forth above, reducing bromotyrosine also would have been "routine" given that phenol was a widely used reagent at the time and known to be capable of reducing free bromine in HBr/acetic acid. (Sept. Tr. (Gokel) 1591:11-1592:13; PTX 961 (Kota Dep. Tr.) at 130:18-131:18.) Reducing amounts of a bromotyrosine impurity thus would have been both a "true" and "routine" production detail at the time of the patent application and did not need to be disclosed to comply with the best mode requirement. *See, e.g*, *Young Dental Mfg. Co.*, 112 F.3d at 1144.

IX. FINDINGS OF FACT AND CONCLUSIONS OF LAW RELATING TO DEFENDANTS' INEQUITABLE CONDUCT DEFENSE

558. Defendants allege that Dr. Pinchasi committed inequitable conduct by failing to submit to the PTO a single page of data containing results of toxicity testing for thirteen batches of copolymer-1 (the "April 1994 Data Table") and failing to inform the PTO of her alleged reservations about the the RBL degranulation test. As set forth below, Defendants have failed to carry their burden of proving inequitable conduct by clear and convincing evidence.

A. Legal Principles

559. To prove inequitable conduct, the accused infringer must establish by clear and convincing evidence that the patent applicant (1) made an affirmative misrepresentation of material fact, failed to disclose material information, or submitted false material information and (2) did so with the intent to deceive the PTO. *Cancer Research Tech. Ltd. v. Barr Labs, Inc.*, 625 F.3d 724, 732 (Fed. Cir. 2010); *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d 1357, 1365 (Fed. Cir. 2008).

560. Intent and materiality are separate elements that must be proven independently by clear and convincing evidence. *Therasense, Inc. v. Becton, Dickinson & Co.*, No. 2008-1511, 2011 WL 2028255, at *10 (Fed. Cir. May 25, 2011) (*en banc*).

561. The Federal Circuit's *en banc* decision in *Therasense* explicitly "tighten[ed] the standards for finding both intent and materiality in order to redirect a doctrine that has been overused to the detriment of the public." *Id.* at *9.

562. With respect to materiality, the Court held that a "but-for" standard applies. *Id.* at 11. In order to assess materiality, "the court must determine whether the PTO would have allowed the claim if it had been aware of the undisclosed reference." *Id.*

563. The Court recognized a narrow exception to the requirement of proving but-for materiality that applies only in "extraordinary circumstances" that amount to "affirmative acts of egregious misconduct" such as the "filing of an unmistakably false affidavit." *Id.* at *12-13. The mere withholding of information or prior art references, however, cannot, as a matter of law, constitute an "affirmative act of egregious misconduct." *Id.* at *12.

564. Undisclosed information that is consistent with statements, data, or representations in a patent is cumulative and therefore cannot be material. *See Impax Labs., Inc. v. Aventis Pharms. Inc.*, 468 F.3d 1366, 1375-77 (Fed. Cir. 2006).

565. With respect to intent, the *Therasense* Court found that an accused infringer must prove "that the applicant knew of the reference, knew it was material, and made a deliberate decision to withhold it." *Therasense*, 2011 WL 2028255, at *9. A specific intent to deceive must be the "single most reasonable inference" able to be drawn from all the evidence. *Id.* at *10 (quoting *Star Scientific, Inc.*, 537 F.3d at 1366). "Indeed, the evidence 'must be sufficient to *require* a finding of deceitful intent in light of all the circumstances.'" *Id.* (quoting *Kingsdown Med. Consultants, Ltd. v. Hollister Inc.*, 863 F.2d 867, 873 (Fed. Cir. 1988)). Where multiple, reasonable inferences could be drawn from the evidence, an intent to deceive cannot be found. *Id.* (citation omitted).

566. *Therasense* also confirmed that an intent to deceive may not be inferred solely from materiality. A court must weigh the evidence of intent to deceive independently from the evidence of materiality. "Proving that the applicant knew of a reference, should have known of its materiality, and decided not to submit it to the PTO does not prove specific intent to deceive." *Id.* (citing *Star Scientific, Inc.*, 537 F.3d at 1366). A weak showing of intent to deceive *cannot* be overcome with a stronger showing of materiality, or vice-versa. *Id.*

B. Findings of Fact

(i) Dr. Pinchasi's Involvement with the '037 Application

567. On May 24, 1994, Mr. Neil Nachshen, an employee in Teva's Patent Department asked Dr. Pinchasi whether she was aware of any publications related to copolymer-1 that were due for publication. (DTX 1393 (Nachshen Dep. 10/13/10) at 11:22-12:4, 20:22-21:7.) Dr. Pinchasi informed Mr. Nachshen that she believed that a paper was to be published that same day in the Proceedings of the National Academy of Sciences (PNAS). (DTX 1393 (Nachshen Dep. 10/13/10) at 20:22-21:7.)

568. Mr. Nachshen confirmed the publication date with PNAS at about 4 p.m. local (Israel) time on May 24, 1994. (DTX 1393 (Nachshen Dep. 10/13/10) at 21:16-23:13.) At that point Mr. Nachshen told others at Teva that they should file a patent application that day, to preserve patent rights in foreign (*i.e.*, non-U.S.) jurisdictions.[8] (PTX 11 at TEV000309430-433; DTX 1393 (Nachshen Dep. 10/13/10) at 20:5-20:14.) That application was filed as U.S. serial no. 08/248,037 ("'037 application").

[8] In the United States, a publication may only qualify as a 35 U.S.C. § 102(b) reference where it described the invention in a "printed publication . . . more than one year prior to the date of the application for patent in the United States." Thus the PNAS disclosure would not have been prior art for the '037 application unless the '037 application had been filed a year after its actual filing date.

569. The ’037 application contains the same Example 2 that appears in the patents-in-suit as described in paragraphs 105-111 above. The ’037 application, however, had different claims from the ones that ultimately issued in later applications that resulted in the patents-in-suit. In particular, the ’037 application had no claims directed to copolymer-1 with an average molecular weight in any particular range. (July Tr. (Pinchasi) at 131:11-23; PTX 10 at TEV003009937.)

570. Mr. Nachshen prepared the ’037 application with the assistance of three other Teva employees, Dr. Pinchasi, Dr. Ralph Haber, and Dr. Ilan Schwartz, in consultation with attorneys from the New York City and Washington, D.C. offices of Kenyon & Kenyon LLP. (DTX 1393 (Nachshen Dep. 10/13/10) at 19:6-13, 20:15-17, 21:7-11, 40:25-41:3, 41:8-12; July Tr. (Pinchasi) 116:9-20, 117:6-11.)

571. Although Mr. Nachshen drafted the majority of the ’037 application, he relied upon others working with him, including Dr. Pinchasi, to provide technical assistance on the subject matter described and claimed in the patent application. (*See e.g.*, DTX 1393 (Nachshen 10/13/2010 Dep.) at 23:20-24:21, 26:10-23, 26:24-27:19.)

572. During the preparation of the ’037 application on May 24, 1994, Dr. Pinchasi provided biological data, specifically *in vivo* and *in vitro* toxicity data, for potential use in the application. (July Tr. (Pinchasi) 117:6-14, 122:4-7.) She did not, however, make the final decision on which data to include in the ‘037 application. (July Tr. (Pinchasi) 146:2-5.)

573. Dr. Pinchasi had never been involved in preparing a patent application before the night of May 24, 1994. (July Tr. (Pinchasi) 122:24-123:4.)

574. Before the ’037 Application was filed on May 24, 1994, Dr. Pinchasi reviewed it and confirmed that it accurately reflected what she knew about the biological toxicity profile of

copolymer-1, as measured by the *in vivo* and *in vitro* toxicity tests described in Example 2. (July Tr. (Pinchasi) 129:1-17.)

(ii) Defendants Proffered No Evidence That Any of the Claims Would Not Have Issued Had the April 1994 Data Table and Dr. Pinchasi's Personal Views About the RBL Test Been Given to the PTO

575. Defendants presented no competent expert evidence at the Inequitable Conduct trial to support a finding that any of the claims in the patents-in-suit would not have issued had the PTO known about the April 1994 Data Table or Dr. Pinchasi's views on the RBL degranulation test.

576. The only evidence proffered by Defendants was a recitation by Defendants' patent expert Mr. Rzucidlo of various communications between Teva and the PTO during prosecution of the patents-in-suit. None of this prosecution history, however, is relevant to the the inequitable conduct claim in this case.

577. Under Defendants' theory, the allegedly withheld toxicity information is related to the issue of unexpected results, which is a secondary consideration of non-obviousness. Unexpected results, however, are only relevant once a claim has been demonstrated to be *prima facie* obvious in view of the prior art. There is no evidence that unexpected results were used to overcome a *prima facie* obviousness rejection based on the '550 patent during prosecution.

578. The first and only obviousness rejection over the '550 patent occurred during the prosecution of the application that resulted in the '808 patent. (*See* PTX 13 at TEV000304138-144.) In response to that rejection, Teva never cited to the data in Example 2 or argued unexpected results to overcome a *prima facie* obviousness rejection. Instead, the examiner withdrew the *prima facie* obviousness rejection noting that the '550 patent did "not fairly suggest, teach or disclose the subject matter embodied" by the allowed claim. (PTX 13 at TEV000304148-52, TEV000304156.) Teva thus was not required to rely on unexpected results

in order to establish the patentability of the '808 patent. (*See* July Tr. (Rzucidlo) 539:9-14, 539:23-541:21, 547:4-550:10.)

(iii) The April 1994 Data Table Was Not Material

579. The April 1994 Data Table, reproduced below, contains batch numbers, molecular weight, and other information for thirteen batches of copolymer-1. (DTX 999A at TEV001222355-RC; DTX 3149T.[9])

אצווה מס'	מולג ממוצע	HPLC פיק SELECT B	% שחרור RBL	SAFETY IN VIVO	SKIN * IRRITATION
123-094	6250	41.0	12.4	0/5	N.T
123-090	7300	43.3	21	0/5	14±2.5 (14±1.2)
123-095	8400	40.8	25.6	0/5	11.6±1.5(12±1.2)
04792	9250	43.9	31.3	0/5	13.8±1(14±1.2)
04892	9600	44.2	50.5 (?)	0/5	N.T.
04992	9900	43.9	51.5 (?)	0/5	13.8±1.2(14±1.2)
123-096	10,950	44.2	39.8	0/5	N.T.
04592	11,050	45.3	41.3	0/5	16±1.2(16.4±0.8)
04692	11,900	45.8	41.7	0/5	N.T.
04492	12,150	47	47.6	0/5	18±1.8(17.2±1)
196/2	13,000	(45.)	66.9	0/5	16.2±1(17±1.55)
196/1	14,500	illegible	67.8	0/5	15.6±0.8(14.8±1)
186/1	22,000	illegible	60.3	3/5	N.T.

580. Dr. Pinchasi was not sure whether she personally created the April 1994 Data Table, but believes it was one of many such summary tables created during the development of copolymer-1 in order to compare chemical and biological data related to different batches. (July Tr. (Pinchasi) 124:13-125:1.)

581. Dr. Pinchasi testified that she may have considered the information in the April 1994 Data Table when she was gathering biological data on May 24, 1994, but she had no specific recollection of doing so. (July Tr. (Pinchasi) 125:2-7.)

[9] DTX 3149-T is a translated version of a single page in DTX 999A.

(1) The April 1994 Data Table is Consistent with Example 2

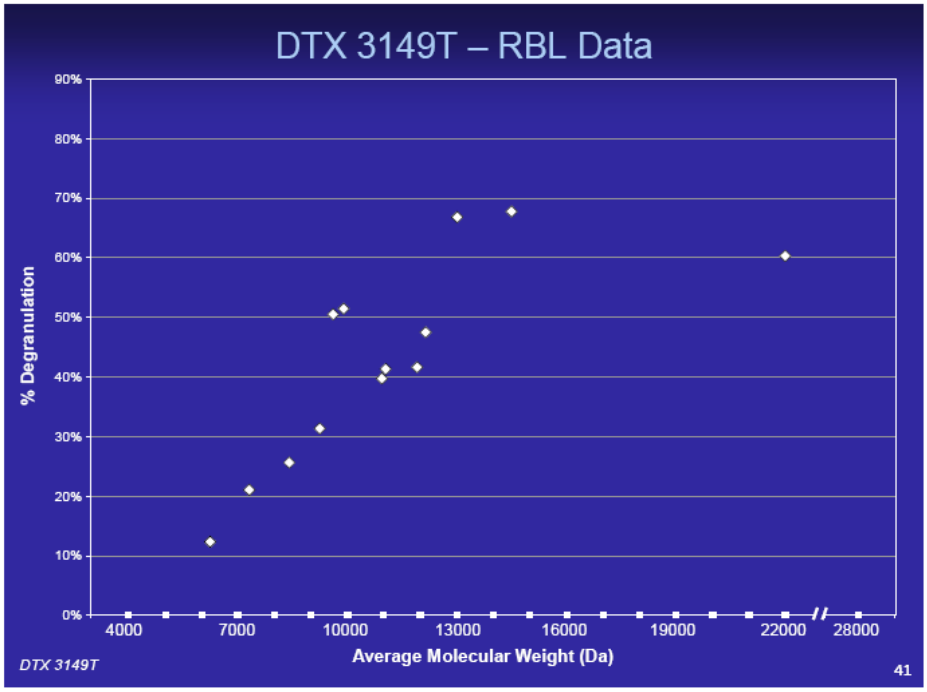
582. Defendants assert that the April 1994 Data Table should have been disclosed to the PTO because, they argue, it is inconsistent with Example 2 of the patent.

583. Example 2 of the patents-in-suit discloses a correlation, or trend, between molecular weight and toxicity. (PTX 1, col. 4:12-27.) As molecular weight increases, toxicity, as shown by percent degranulation in the RBL test, increases. (July Tr. (Baird) 600:7-14.)

584. The evidence showed that the data in the April 1994 Data Table is consistent with the trend disclosed in Example 2 of the patents.

585. Dr. Baird, a recognized expert in the RBL degranulation test, took the molecular weight and RBL degranulation data contained in the April 1994 Data Table and plotted them on the graph shown in Figure 26 below. She found that the data in the April 1994 Data Table show the same trend as seen in Example 2 -- increasing RBL degranulation with increasing molecular weight. (July Tr. (Baird) 603:7-604:5; PTX 887 at 40.)

Figure 26



586. Dr. Pinchasi likewise testified that the data in the April 1994 Data Table "very clearly and strongly supports the correlation we have discussed – the higher the average molecular weight, the higher percentage of RBL release." (July Tr. (Pinchasi) 125:14-19.)

587. Even Defendants' expert Dr. Kimber conceded that the RBL data in the April 1994 Data Table, like all of the other data he has seen in this case, reflect a trend of increasing RBL degranulation with increasing average molecular weight. (July Tr. (Kimber) 446:22-447:15, 465:2-3, 466:10-19.)

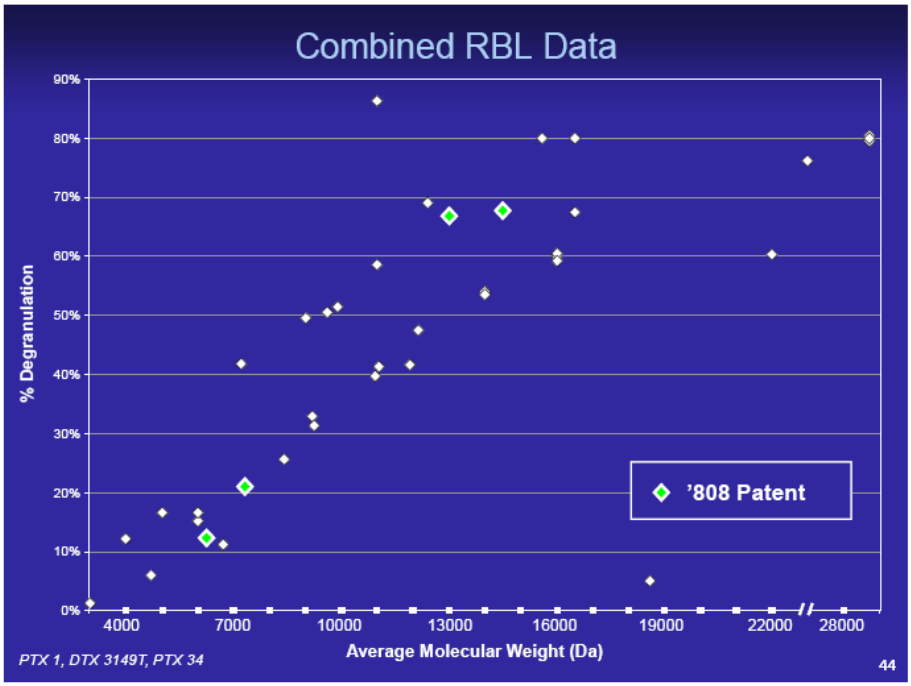
(2) Example 2 is Representative of Teva's Toxicity Data as a Whole

588. The Weizmann and Teva scientists performed hundreds of RBL degranulation tests on batches of copolymer-1 during development of the product. (July Tr. (Arnon) 332:8-334:2; *see, e.g.*, PTX 34T; PTX 36T; PTX 53T; PTX 54.) The April 1994 Data Table contains only a small fraction of those test results.

589. The evidence showed that the data in Example 2 of the specification was a fair and accurate representaion of the data generated by the Teva and Weizmann scientists as a whole. (July Tr. (Arnon) 332:8-334:2; July Tr. (Pinchasi) 30:14-20, 80:13-81:13; July Tr. (Baird) 601:13-24; PTX 887 at 44.)

590. Dr. Baird took molecular weight and RBL degranulation data for several different batches of copolymer-1 found in Teva's internal files for several different batches of copolymer-1 that had been cited by Defendants' experts and added them to the graph she had created for the data in the April 1994 Data Table.

Figure 27



591. She again found that the data showed "a very clear trend" consistent with the trend shown in Example 2. (July Tr. (Baird) 601:13-24, 605:14-18; PTX 887 at 44.)

592. Teva and Weizmann's *in vivo* toxicity data is similarly consistent with Example 2, and Defendants provided no expert testimony to the contrary. Although the only copolymer-1 batch in the April 1994 Data Table that failed the *in vivo* toxicity test had a molecular weight of 22,000 daltons, Teva and Weizmann had internal data on many batches of copolymer-1 with molecular weights between 10,000 and 22,000 daltons that had failed that test. (July Tr. (Pinchasi) 126:4-8; *see, e.g.*, PTX 34-T.)

593. Defendants did not provide their expert Dr. Kimber with all of the RBL degranulation and *in vivo* mouse test data that had been produced by Teva in this case. (July Tr. (Kimber) 426:21-429:16, 438:13-439:1.) Accordingly, Dr. Kimber did not know whether the data in the April 1994 Data Table reflected the universe of toxicity data that had been generated

by Weizmann and Teva, and could not provide an opinion on whether Teva's data as a whole was consistent with Example 2. (July Tr. (Kimber) 438:18-439:5.)

(3) The Patent Office Was Aware That Not All High Molecular Weight Copolymer-1 Batches Were Toxic

594. Plaintiffs assert that Teva represented to the PTO in Example 2 that all batches of copolymer-1 above 10,000 daltons were toxic, and that the April 1994 Data Table shows otherwise. This is also incorrect.

595. As Dr. Baird testified, Example 2 describes a trend showing increasing toxicity with increasing molecular weight. (July Tr. (Baird) 600:7-23.) It does not state or imply that all batches above 10,000 daltons were toxic and all batches below were not. (July Tr. (Baird) 600:7-23.)

596. In fact, Example 2 explicitly concludes that "[a]s can be seen, when the % of high molecular weight species is low (<2.5), the % release of serotonin indicative of toxicity is low, and vice versa." (PTX 1, col. 4:25-27.) As Dr. Baird explained, this statement indicates a trend in the data, not any hard cut-off. (July Tr. (Baird) 600:7-14.)

597. Momenta's own scientists outside the context of this litigation understood that the data in Example 2 showed a trend. An internal report discussing the patents-in-suit states that the Momenta scientists found that "the higher the Average Molecular Weight, the greater the percent serotonin released." (PTX 186 at MMT00950946.)

598. Moreover, Dr. Bornstein's 1987 article, cited in the specifications of the patents-in-suit, explicitly states that some batches of copolymer-1 having a molecular weight of between 14,000 and 23,000 daltons showed less than 30% degranulation in the RBL assay, *i.e.*, were "non-toxic." (PTX 1, col. 1:25-28; PTX 11 at TEV000309437; PTX 31 at 408-09.) The file histories indicate that the PTO examiner reviewed and considered the Bornstein article during

the prosecution of the patents-in-suit. (PTX 18 (File History of U.S. Patent 6,362,161 ("'161 File History")) at TEV000310385-389; PTX 14 (File History of U.S. Patent No. 5,981,589 ("'589 File History")) at TEV000309018-21; PTX 21 (File History of U.S. Patent No. 7,199,098 ("'098 File History")) at TEV000308838-842.)

599. Thus, the PTO was well aware from both the specification and prosecution of the patents that not all higher molecular weight copolymer-1 batches were toxic. Any such information in the April 1994 Data Table would have been cumulative.

(iv) Dr. Pinchasi's Views on the RBL Degranulation Test Were Not Material

(1) Dr. Pinchasi Believed the RBL Degranulation Test To be a Reliable Screening Test for Toxicity

600. In a December 1989 memo, Dr. Pinchasi set forth her rationale for adopting a second screening test, the *in vivo* toxicity test, in addition to the RBL degranulation test. (DTX 3385.) Defendants point to this memo as evidence that Dr. Pinchasi believed that the RBL test could not be used as a toxicity screen. That conclusion cannot be drawn.

601. As Dr. Pinchasi explained, she believed that the RBL degranulation test was "very good" for screening toxic batches during process development, but that she "didn't think it was sufficiently reproducible to [serve] as a sole, as a single, an only methodology to be used to decide whether a batch is safe for clinical use or not." (July Tr. (Pinchasi) 102:24-103:17.)

602. Teva decided to use both the RBL degranulation test and the *in vivo* toxicity test because they viewed them as complementary in terms of how they can be used to predict clinical safety. (July Tr. (Pinchasi) 29:1-19, 103:9-20.)

603. The Court credits Dr. Pinchasi's testimony that, despite some concerns about using the RBL degranulation test as the only test for clinical use, she and others at Teva

continued to use that test to draw conclusions about the toxicity of batches of copolymer-1. (July Tr. (Pinchasi) 102:24-104:1, 104:16-20.)

604. Dr. Pinchasi's testimony is corroborated by internal Teva documents showing that Teva continued to use the RBL degranulation assay in conjunction with the *in vivo* toxicity test for many years after Dr. Pinchasi's December 1989 memo was written. (July Tr. (Pinchasi) 101, 103:18-104:15; PTX 723.)

605. For example, a December 1990 FDA submission contains data on both RBL degranulation testing and *in vivo* toxicity testing performed on the same batches in May 1990. At that time, the RBL degranulation test was being used routinely by Teva and the Weizmann Institute to screen batches of copolymer-1. (July Tr. (Pinchasi) 95:21-97:9, 101; 103:18-104:15; PTX 723 at TEV000599237, 241, 245, 249, 253, 257, 260.)

606. The RBL degranulation test was still being used by the Weizmann Institute and Teva at least through December 1992. (July Tr. (Pinchasi) 99:5-100:3; PTX 62.)

(2) Professor Arnon Believed the RBL Degranulation Test to Be a Reliable Screening Test for Toxicity

607. The RBL degranulation test was not selected by Dr. Pinchasi. Inventor Professor Arnon selected the test after concluding that it was an appropriate assay for screening batches of copolymer-1 for toxicity. Even after Teva took on development of copolymer-1, the RBL testing continued to be performed at the Weizmann Institute. (July Tr. (Pinchasi) 30:7-20; July Tr. (Arnon) 332:8-25; July Tr. (Baird) 608:25-609:10.)

608. Before making the decision to adopt the RBL degranulation test, Professor Arnon personally read all the literature about the test, including articles by Dr. Reuben Siraganian's group at NIH, who were the leading experts on the test. (July Tr. (Arnon) 321:19-25.)

609. One of the literature references that Professor Arnon considered was a 1981 article ("the Barsumian article") by Dr. Barsumian, who was a member of the Siraganian group at NIH. The Barsumian article reported that the RBL degranulation test had a reproducibility of approximately 20%. (July Tr. (Arnon) 325:14-326:1; PTX 522 at 320.) Given this data, Dr. Barsumian concluded that the test was "quite reproducible." (July Tr. (Arnon) 321:19-326:13, 337:7-16; PTX 522 at 322.)

610. Based on the literature available at the time and Professor Arnon's experience with biological assays, she and her colleagues at the Weizmann Institute determined that the RBL degranulation test, with its approximately 20% reproducibility, was "quite reliable." (July Tr. (Arnon) 321:8-326:25, 336:2-337:17; PTX 522; PTX 711; DTX 3114.)

611. Weizmann and Teva's protocol for performing the RBL degranulation test was contained in a specification that had been drafted, not by Dr. Pinchasi, but by Weizmann scientist Dr. Teitelbaum. Professor Arnon reviewed the RBL specification. (July Tr. (Pinchasi) 89:23-91:4; July Tr. (Arnon) 334:14-23; DTX 3114.) The RBL specification was later signed and approved by Dr. Pinchasi. (July Tr. (Pinchasi) 89:23-91:4; DTX 3114.)

612. According to the RBL specification drafted by Dr. Teitelbaum, the RBL degranulation test was used "to screen out those batches of cop-1 which evoke substantial degranulation and thus might elicit undesirable local and/or systemic side effects." (DTX 3114 at TEV000881362.) As Professor Arnon testified, she still believes today that this is an accurate statement of the appropriate use of the RBL degranulation test. (July Tr. (Arnon) 334:24-335:14.)

613. The RBL specification shows that the test was validated, meaning that it was proven to be precise and reproducible enough for the purposes for which it was being used. (July

Tr. (Pinchasi) 92:22-93:17; DTX 3114 at TEV000881368.) The precision of the RBL degranulation test (in terms of its relative standard deviation ("RSD")) was reported as ± 19%, and its reproducibility (in terms of RSD) was reported as ± 26%. (July Tr. (Pinchasi) 94:9-15; DTX 3114 at TEV000881368-369.) Professor Arnon testified that this level of precision and reproducibility was both accceptable and within the range of what the Weizmann scientists expected. (July Tr. (Arnon) 336:2-337:6.)

(3) The RBL Degranulation Test Described in the Patent is a Well-Accepted Test in the Scientific Community

614. Dr. Baird testified at trial that the RBL degranulation test is a very reliable and reproducible test that is widely used by the scientific community as a model for immediate hypersensitivity that might occur in humans. (July Tr. (Baird) 585:9-21, 595:4-16, 596:25-597:8, 610:6-20, 611:15-22; PTX 522.)

615. Dr. Baird specifically testified that she agreed with the description of the RBL test set out in the patent, and believes it was reasonable for the Weizmann Institute and Teva scientists to use the test for the purpose described in the patent -- to "screen out those batches of copolymer-1 which evoke substantial degranulation and thus might elicit undesirable local and/or systemic side effects." (July Tr. (Baird) 593:21-597:8.)

616. This language in the patent was taken directly from the RBL specification written by the scientists at the Weizmann Institute. (July Tr. (Pinchasi) 286:11-288:16; PTX 1, col. 3:63-67; PTX 10 at TEV003009934; DTX 3114 at TEV000811362.)

617. In fact, Defendants themselves have performed RBL degranulation testing and have acknowledged its acceptance in the scientific community.

618. Dr. Bhujanga Rao, defendant Natco's President of Research and Development, testified that Natco performed RBL degranulation testing, and that the RBL degranulation test is

a "well-known toxicity test for hypersensitivity reactions to products" that is "predictive of hypersensitivity in humans." (PTX 883 (Rao Dep.) at 149:22-150:4.)

619. [redacted]

620. Although Defendants' expert Dr. Kimber testified that the RBL degranulation test is not sufficiently reproducible to draw any conclusions about the toxicity of copolymer-1, he has limited experience with the test, and has never performed that test himself. (July Tr. (Kimber) 426:1-3, 426:8-17.) His testimony was based entirely on the variability for the test described in the RBL specification. [redacted]

621. The fact that the Bornstein article, which appeared in the New England Journal of Medicine and was peer-reviewed, explicitly describes the use of the RBL degranulation test as a toxicity screen for copolymer-1 batches is further evidence that use of the test would have been generally accepted by the scientific community. (July Tr. (Arnon) 329:3-331:4; PTX 31 at 409.)

(4) The Patent Office Knew About The Reproducibility Of The RBL Degranulation Test

622. Example 2 of the patents-in-suit cites to the same two literature references cited in the RBL specification–the Barsumian and Siraganian articles. The Barsumian article specifically reported a reproducibility of ± 20% for the RBL degranulation test. (PTX 1, col. 3:50-55; PTX

522.) Thus, the examiner was aware of the reproducibility of the test when making the decision to allow the claims to issue.

(v) There is No Evidence of Intent to Deceive

(1) Dr. Pinchasi Testified Credibly That She Had No Intent to Deceive the PTO

623. Dr. Pinchasi testified directly that she had no intention of deceiving the PTO when she supplied the biological data for the '037 patent application. (July Tr. (Pinchasi) 135:6-22.)

624. As she explained, when she reviewed the '037 application, she believed that the *in vivo* data reported in Example 2A was representative of the accumulated Weizmann data she was aware of at that time. She also believed that there was a correlation between *in vivo* toxicity measured by the test set forth in Example 2 and the molecular weight of copolymer-1 as set forth in Example 2. (July Tr. (Pinchasi) 129:14-130:1, 135:6-22.)

625. Dr. Pinchasi similarly testified that Example 2B accurately reflects what she knew in 1994 and still believes today—that there is a correlation between the average molecular weight of copolymer-1 and toxicity measured by the *in vitro* RBL test set forth in Example 2. (July Tr. (Pinchasi) 130:5-131:8, 135:6-22.)

626. Dr. Pinchasi also testified that she believed then, and continues to believe, that the RBL degranulation test was sufficiently reliable and reproducible for the purposes for which it was used at Teva, including establishing the correlation between molecular weight and toxicity for copolymer-1. (July Tr. (Pinchasi) 95:13-20, 104:16-20.)

627. Dr. Pinchasi's testimony as set forth above was credible and supports a finding that she did not act with intent to deceive.

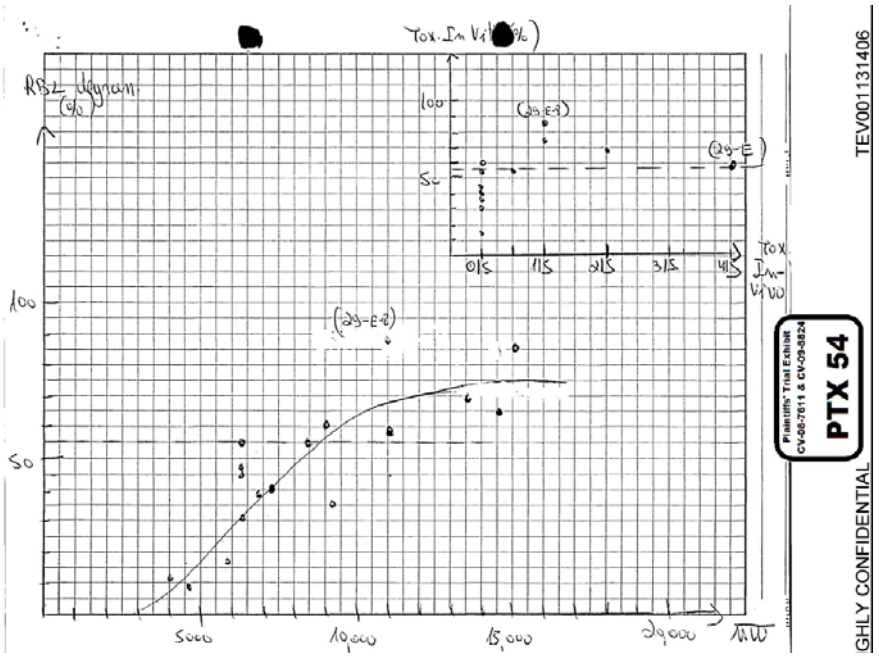
(2) Dr. Pinchasi's Contemporaneous Documents Establish Good Faith

628. Dr. Pinchasi's testimony is corroborated by contemporaneous documents, which establish that she truly believed that there was a correlation between molecular weight and toxicity for copolymer-1, and that it was necessary to lower the molecular weight range of copolymer-1 to approximately 5,000 to 9,000 daltons in order to have the best chance for an active, non-toxic product.

629. In particular, Dr. Pinchasi testified about a series of graphs she created in around April 1988 that demonstrated the correlation between molecular weight and toxicity that her team had discovered.

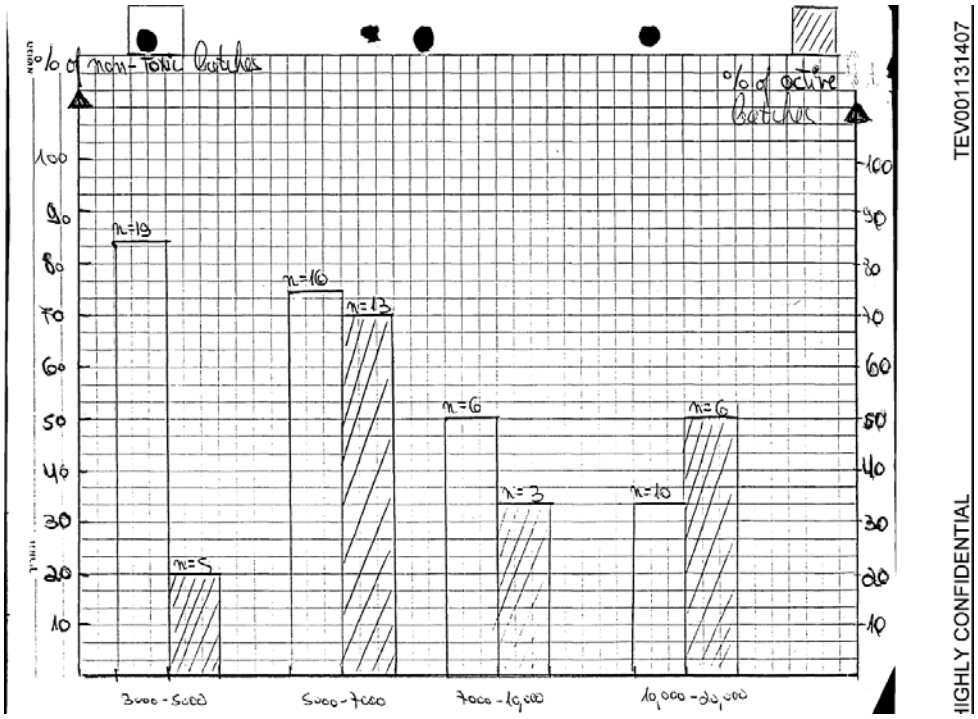
630. For example, in the graph in the lower left hand corner of Figure 28 below, Dr. Pinchasi plotted RBL degranulation percent vs. molecular weight for several different copolymer-1 batches. As Dr. Pinchasi testified, and as can be seen in the graph, the data showed an almost linear correlation between molecular weight and toxicity. (July Tr. (Pinchasi) 46:21-48:24; PTX 54 at TEV001131406.)

Figure 28



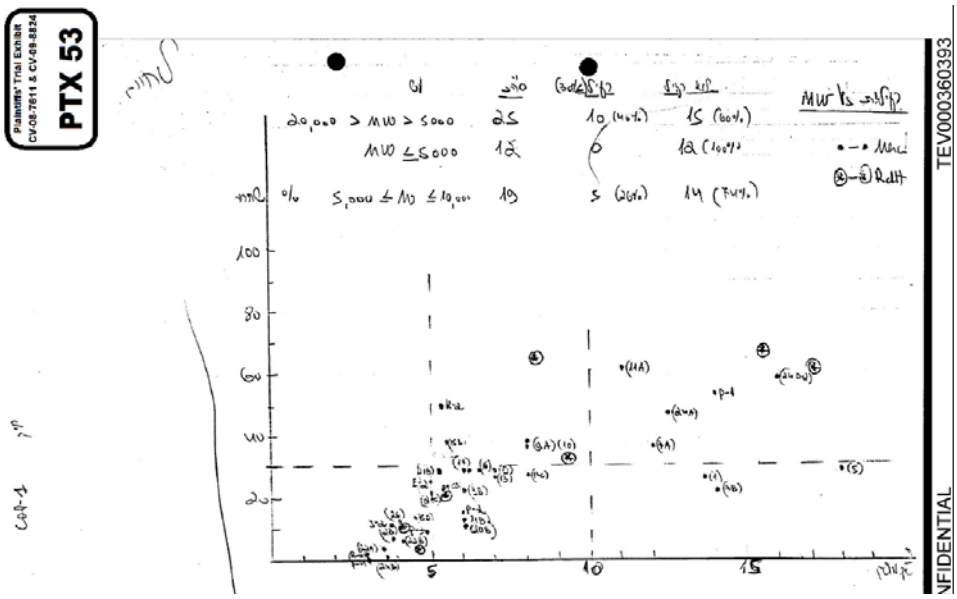
631. In Figure 29 below, Dr. Pinchasi created a bar graph that plotted the percent of copolymer-1 batches that were non-toxic and active in different molecular weight ranges. As Dr. Pinchasi testified, and as the bar graph shows, the range from 5,000 to 7,000 daltons gave the highest proportion of batches that were both non-toxic and active. (July Tr. (Pinchasi) 51:20-53:19; PTX 54 at TEV001131407.)

Figure 29



632. Dr. Pinchasi also testified about the plot of RBL degranulation percent vs. molecular weight for several batches of copolymer-1 shown in Figure 30 below. (July Tr. (Pinchasi) 57:2-61:13; PTX 53 at TEV000360393; PTX 53-T at TEV000360393.) This graph again showed that there was a correlation between molecular weight and toxicity, and that a molecular weight range of 5,000 to 9,000 daltons provided the best chance for a batch of copolymer-1 to be active and non-toxic. (July Tr. (Pinchasi) 57:15-59:23.)

Figure 30



633. In fact, Defendants' expert Dr. Kimber agreed with Dr. Pinchasi's assessment that the graph in Figure 30 above shows a trend in the data of increasing toxicity with increasing molecular weight. (July Tr. (Kimber) 429:10-430:8.)

634. Dr. Pinchasi reported these conclusions in contemporaneous memoranada and correspondence. For example, in a May 1988 status report, Dr. Pinchasi reported that the molecular weight range of 15,000 to 25,000 daltons that had been used in the past by the Weizmann researchers yielded a majority of batches that were toxic in the RBL degranulation test, and that "the optimum range for an active and nontoxic material is 6000-9000." (July Tr. (Pinchasi) 39:18-41:24; PTX 41 at 2.)

635. Similarly, in an April 14, 1988 memo, Dr. Pinchasi characterized low-molecular weight (3,000-6,000 daltons) batches of copolymer-1 as "non-toxic" and high-molecular weight (10-25,000 daltons) batches as "toxic." (PTX 35 at TEV000360388; PTX 35-T at TEV000360388; July Tr. (Pinchasi) 43:21-45:6.)

636. In a June 27, 1988 quarterly report, Dr. Pinchasi reported that "[a]n unequivocal correlation was found between molecular weight and in vitro toxicity of COP-1: the higher the molecular weight-the more toxic is the drug. This relationship was correlated on several batches prepared both at the Weizmann Institute and at Bio-Yeda." Dr. Pinchasi concluded in the report that "[i]n order to produce a nontoxic material, its molecular weight should be < 10,000 and not 15,000 to 25,000 as declared in the Bio-Yeda chemical file (submitted to the FDA February of '86)." (July Tr. (Pinchasi) 69:1-71:10; PTX 40 at 1.)

637. In a July 25, 1988, letter to Dr. Bornstein, Dr. Pinchasi similarly reported that Teva had "found a very strong positive correlation between molecular weight and toxicity" that was "unequivocal." (July Tr. (Pinchasi) 71:25-74:3; PTX 42 at 1.)

638. These conclusions were later summarized in a 1991 report by inventor Mr. Konfino: "In the early period of development the data on the many samples of COP-1 . . . were gathered together and the distribution of their toxicity and bio-activity versus the molecular weight were laid down on a milimetric paper. It was found that the largest number of satisfactory samples were crowded in the relatively narrow section between molecular weight 5000-7000. The specification for MW of COP-1 was thus fixed as 6000±1000 . . ." (July Tr. (Pinchasi) 79:14-81:22; PTX 708 at TEV000324552; PTX 708-T at TEV000324552.)

(3) Dr. Pinchasi Had No Motive to Lie to the PTO

639. Defendants have asserted that Dr. Pinchasi had a motive to lie to the PTO because she needed to obtain a patent covering Copaxone® in order to bring the product to market. The evidence is to the contrary.

640. As Dr. Pinchasi testified, when Teva began work on the copolymer-1 project, it knew that the Weizmann Institute's '550 patent on copolymer-1 was going to expire before a product could be brought to market. Teva decided to proceed with the project anyway, because

it developed strategies that it believed could protect exclusivity in the marketplace even without having a patent on the product. (July Tr. (Pinchasi) 19:12-22:3, 117:22-118:8.)

641. Teva assumed that copolymer-1 would be entitled to orphan drug exclusivity, which was established by the U.S. government to encourage pharmaceutical companies to develop drugs for diseases with fewer than 200,000 patients. Orphan drug exclusivity provides seven years of exclusivity from the time a product reaches the market regardless of whether the product is covered by a patent. Teva was in fact eventually awarded orphan drug exclusivity for Copaxone®. (July Tr. (Pinchasi) 20:22-21:23; PTX 41-A at 5.)

642. Teva also knew that copolymer-1 would be difficult to manufacture reproducibly in a commercial pharmaceutical context. (July Tr. (Pinchasi) 19:23-20:21.)

643. Moreover, there is no evidence that the lack of patent protection for copolymer-1 was ever an issue during development of Copaxone®. On the contrary, the evidence showed that Teva was prepared to go to market with Copaxone® without patent protection.

644. As Dr. Pinchasi testified, she could not remember the subject of patent protection ever coming up at a meeting concerning the development of copolymer-1. (July Tr. (Pinchasi) 117:18-21, 118:20-25.)

645. Dr. Pinchasi's testimony was corroborated by her handwritten memo summarizing a June 5, 1991 discussion concerning a copolymer-1 Go/No Go meeting. (July Tr. (Pinchasi) 106:20-24, 118:20-121:22; PTX 57; PTX 57-T.) As Dr. Pinchasi testified, in Teva's terminology a Go/No Go meeting was a meeting at which a decision was taken on whether to abort a project or continue development. (July Tr. (Pinchasi) 106:20-24.) Dr. Pinchasi's memo contained a thorough list of all of the critical issues that existed at that time with respect to the development of copolymer-1. Lack of patent protection for copolymer-1 was not mentioned in

the memo and was not discussed at the Go/No Go meeting. (July Tr. (Pinchasi) 118:20-121:22; PTX 57; PTX 57-T.)

646. Significantly, at the time Teva filed its NDA for Copaxone® it did not have an issued patent, and it did not know whether it would ever have patent protection for the product. (July Tr. (Pinchasi) 118:9-19.)

647. Dr. Pinchasi's lack of motive to withhold the April 1994 Data Table from the PTO is further demonstrated by the fact that the claims in the '037 patent application when Dr. Pinchasi reviewed it on the night of May 24, 1994 did not have any average molecular weight limitations. They were directed, instead, to the percent of species above 40 kilodaltons or the percent of species between 2 and 20 kilodaltons. The April 1994 Data Table, on the other hand, had average molecular weight information, but no information about percent species in those ranges. The April 1994 Data Table, therefore, would not have contained any information relevant to the patentability of those claims. (July Tr. (Pinchasi) 131:20-132:8; July Tr. (Kimber) 478:4-15; DTX 3149T; PTX 10 at TEV003009937.)

(4) Dr. Pinchasi Did Not Take Inconsistent Positions With the FDA and PTO

648. Defendants assert that Dr. Pinchasi's intent to deceive is demonstrated by the fact that she took different positions concerning molecular weight and toxicity before the PTO and the FDA. The evidence was otherwise.

649. Neither Dr. Pinchasi nor Teva took a position with the FDA that contradicted or was inconsistent with the toxicity data in Example 2 of the patents-in-suit.

650. Teva represented to the FDA that the low average molecular weight copolymer-1 compositions were, in certain respects, comparable to the high average molecular weight copolymer-1 compositions used by Dr. Bornstein in his clinical trial. Teva's statements to the

FDA about *safety*, however, are not inconsistent with what Teva told the PTO about the *toxicity* of high molecular weight copolymer-1.

651. As Defendants' expert Dr. Green testified, safety and tolerability are two different concepts. Dr. Green explained that two drugs can be equally safe, yet have different tolerability profiles. (PTX 881 (Green Dep.) at 16:12-17:04.)

652. The local and systemic side reactions that the toxicity testing in the patent are intended to screen for are related to the *tolerability* and *not the safety* of copolymer-1. (July Tr. (Arnon) 315:7-15; July Tr. (Pinchasi) 26:2-14; PTX 881 (Green Dep.) at 16:12-25.)

653. As Dr. Green acknowledged, Teva did not make any representations to the FDA that the *tolerability* of low average molecular weight copolymer-1 was the same as the prior art high average molecular weight copolymer-1. (PTX 881 (Green Dep.) at 17:1-4, 111:11-24.)

654. Moreover, the Bornstein article, which was incorporated by reference in the specification of the patents-in-suit, described the use of high average molecular weight copolymer-1 in human patients and stated that it was shown to be non-toxic in animal studies. (PTX 1, col. 1:25-28; PTX 31 at 4081.) Thus, the PTO was aware that high molecular weight copolymer-1 was "safe" for use in humans.

C. Conclusions of Law

655. In order to prove that Dr. Pinchasi committed inequitable conduct, Defendants bear the burden of proving both materiality and intent to deceive by clear and convincing evidence. They have failed to do so.

(i) Defendants Failed to Establish the Materiality of the April 1994 Data Table and the RBL Degranulation Information

656. As an initial matter, Defendants are required to prove materiality under the "but-for" standard articulated in *Therasense*. 2011 WL 2028255, at *12. Defendants have not alleged

any affirmative misconduct on the part of Dr. Pinchasi. Their only claim is that she withheld information from the PTO. As a matter of law, the withholding of information cannot amount to an "exceptional case" involving "affirmative acts of egregious misconduct." *Id.* at *12-13.

657. To prove materiality under the "but-for" standard, Defendants were required to prove that the PTO office would not have allowed at least one claim in each of the patents-in-suit to issue had it been aware of the April 1994 Data Table and Dr. Pinchasi's views on the RBL degranulation test. *Id.* at *12.

658. Under Defendants' theory, the allegedly withheld toxicity information is related to the issue of unexpected results, which is a secondary consideration of non-obviousness. Unexpected results, however, are only relevant once a claim has been demonstrated to be *prima facie* obvious in view of the prior art. *See In re Oetiker*, 977 F.2d 1443, 1446 (Fed. Cir. 1992) ("If examination at the initial stage does not produce a prima facie case of unpatentability, then without more the applicant is entitled to grant of the patent." (citations omitted)); *In re Fischer*, 484 F.2d 961, 963-64 (C.C.P.A. 1973) (holding that appellant need not show unexpected results because Patent Office failed to make out a prima facie obviousness case).

659. Thus, to establish that the April 1994 Data Table and other information were material to the claims of the patents-in-suit, Defendants were first required to introduce evidence proving that the claims were *prima facie* obvious. This obviousness analysis must be performed on a claim-by-claim basis and from the viewpoint of a person of ordinary skill in the art. 35 U.S.C. § 282; *KSR Int'l Co.*, 550 U.S. at 406.

660. Defendants, however, introduced *no* competent expert tesimony during the inequitable conduct trial that any one of the asserted claims would have been found *prima facie* obvious in view of the prior art. Instead, Defendants ask the Court to make obviousness

determinations based solely on attorney argument regarding the prosecution history. Attorney argument, however, is insufficient. *See Invitrogen Corp. v. Clontech Labs.*, 429 F.3d 1052, 1068 (Fed. Cir. 2005). In any event, as discussed above, the prosecution history does not support Defendants' contentions.

661. Defendants' failure of proof precludes a finding that the allegedly withheld information was material.

662. Even if the toxicity data in the patent were required to establish the patentability of any claim of the patents-in-suit (which they are not), the April 1994 Data Table and Dr. Pinchasi's views on the RBL degranulation test would not be material because they are consistent with, and therefore cumulative of, both Example 2 of the patents and other information provided to the PTO during prosecution. *See Honeywell Int'l Inc. v. Universal Avionics Sys. Corp.*, 488 F.3d 982, 1000 (Fed. Cir. 2007).

663. The April 1994 Data would also not be material because it represents only a small fraction of Teva's data, and Teva's data as a whole is consistent with Example 2. (July Tr. (Arnon) 332:8-334:2; July Tr. (Pinchasi) 30:14-20, 80:13-81:13; July Tr. (Baird) 601:13-24; PTX 887.)

664. Moreover, even if Dr. Pinchasi did have reservations about the RBL degranulation test, there is no evidence those reservations were shared by anyone else. To the contrary, the evidence shows that the RBL degranulation test is a widely accepted test in the scientific community, including by Defendants' own scientists, and the description of it in the patent is in line with both how it was used at Teva and the Weizmann Institute, and how the literature had reported that it could be used. Significantly, inventor Professor Arnon personally held the view then, and still holds the view, that the test is reliable and reproducible enough to

screen batches of copolymer-1 for toxicity. (July Tr. (Pinchasi) 286:11-288:16; July Tr. (Arnon) 320:7-321:18, 327:22-331:4; July Tr. (Kimber) 466:20-468:21, 471:16-18, 472:4-475:6; PTX 31 at 409; DTX 1334 at 345.)

665. If the literature, such as the Barsumian article, which is cited in the patent itself, reports that the RBL test with a precision of ±20% is reliable and reproducible, and the inventor herself believes this to be the case, it is not plausible that Dr. Pinchasi's personal views would have prevented any of the claims from issuing.

666. Finally, even if the RBL degranulation test data was not sufficiently reproducible to be relied upon (a conclusion the Court is not reaching), Defendants presented no evidence that the *in vivo* mouse data in Example 2 would have been insufficient to demonstrate the patentability of any claim of the patents-in-suit. In fact, Defendants presented no expert testimony at all regarding the *in vivo* mouse assay during the July 2011 trial. Defendants' expert Dr. Rice testified only during the September 2011 trial and, as the Court ruled during trial, Dr. Rice's testimony could not be relied on to prove inequitable conduct. (Sept. Tr. (Rice) 1029:7-20, 1032:8-21.)

667. Thus, Defendants have failed to prove by clear and convincing evidence that any of the information or data they allege was withheld was material.

(ii) Defendants Failed to Establish that Dr. Pinchasi Had An Intent to Deceive the PTO

668. Defendants have proffered no direct evidence that Dr. Pinchasi had an intent to deceive the PTO, and they have failed to introduce any evidence from which an inference of an intent to deceive could be drawn.

669. On the contrary, Dr. Pinchasi's testimony established that she believed and believes to this day that there is a correlation between the average molecular weight of

copolymer-1 compositions and their potential to cause toxicity in the RBL degranulation assay and the *in vivo* mouse toxicity assay, and that the data in Example 2 accurately reflects this correlation. (July Tr. (Pinchasi) 135:6-22.) The Court credits Dr. Pinchasi's testimony, and her testimony is corroborated by her contemporaneous documents.

670. Circumstantial evidence also supports the conclusion that Dr. Pinchasi acted in good faith. Had Dr. Pinchasi deliberately sought to conceal from the PTO examiner the fact that high molecular weight batches could show low toxicity, as Defendants contend, the very first page of the '037 application would not reference and incorporate Dr. Bornstein's 1987 article, which describes copolymer-1 compositions with average molecular weights of about 14,000 to 23,000 daltons as inducing less than 30% degranulation. (PTX 31 at 408-09.)

671. The evidence also showed that Dr. Pinchasi lacked any motive to intentionally deceive the PTO. As Dr. Pinchasi credibly testified, the copolymer-1 project did not hinge on getting patent protection for Copaxone®. Teva entered into the project, and continued to develop the product, with the expectation that it would not have such protection. (July Tr. (Pinchasi) 19:23-22:3, 117:22-118:8, 295:12-17; PTX 41A.)

672. Dr. Pinchasi also did not provide any contradictory or inconsistent information to the PTO and the FDA regarding the toxicity and safety of the claimed low average molecular weight copolymer-1 compositions. as compared to those used in the Bornstein clinical trial, since safety and tolerability are different concepts. Moreover, intent cannot be inferred when Teva disclosed numerous references containing substantially the same substantive information as was provided to the FDA during prosecution of the patents. *Rothman v. Target Corp.*, 556 F.3d 1310, 1328 (Fed. Cir. 2009) (submission of letters discussing two prior art styles negates any inference of an intentional deception in failure to submit same prior art).

673. Thus, Defendants have failed to prove clearly and convincingly that Dr. Pinchasi intended to deceive the PTO.

674. As Defendants have failed to prove either materiality or intent to deceive by clear and convincing evidence, their inequitable conduct defense must be dismissed.

X. FINDINGS OF FACT AND CONCLUSIONS OF LAW RELATING TO DEFENDANTS' OBVIOUSNESS DEFENSE

675. Defendants also argue that the claims-in-suit would have been obvious to a person of ordinary skill in the art as of May 24, 1994, the filing date of the '037 application. In making this argument, Defendants focus on two categories of limitations in the asserted claims. First, Defendants argue that copolymer-1 falling within the claimed average molecular weight ranges, or having the claimed molecular weight distribution, would have been obvious. Second, Defendants argue that certain process limitations for making copolymer-1 – in particular the use of HBr in acetic acid to achieve the desired molecular weight – would have been obvious. Defendants have failed, however, to focus on the claims as a whole, as is required to establish obviousness. Even limiting the analysis to the limitations for which Defendants presented evidence, Defendants have failed to present clear and convincing evidence that either the molecular weight or process limitations of the claims of the patents-in-suit would have been obvious to a person of ordinary skill in the art as of May 24, 1994.

A. Legal Principles

676. To succeed on their obviousness claims, Defendants must prove by clear and convincing evidence that "the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103; *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006). The clear and convincing standard is a heightened standard of proof, and a defendant raising an invalidity defense bears "a heavy

burden of persuasion." *Microsoft Corp.*, *131 S. Ct.* . at 2246-47. "When, as here, a party asserts invalidity of a patent and bases that assertion on evidence, including prior art references, that was before the patent examiner when he allowed the patent claims, the difficulty of overcoming the presumption of validity is greater than it would be if the evidence relied on was not before the examiner." *In re Omeprazole Patent Litigation*, 490 F. Supp. 2d at 500 (citing *Am. Hoist & Derrick Co. v. Sowa & Sons*, 725 F.2d at 1358-60 (Fed. Cir. 1984)). "In determining whether to allow the application, the patent examiner is also presumed to have considered each reference that was before him individually and in combination with every other reference before him." *Astra Aktiebolag v. Andrx Pharmaceuticals, Inc.*, 222 F. Supp. 2d 423, 562 (S.D.N.Y. 2002), *aff'd sub nom*, *In re Omeprazole Patent Litig.*, 84 Fed. Appx. 76 (Fed. Cir. 2003) ; *see also Microsoft Corp.*, 131 S. Ct. at 2250.

677. To determine whether a claim is obvious, the Court must consider: "(1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) evidence of secondary factors, also known as objective indicia of nonobviousness." *Eisai Co. v. Dr. Reddy's Labs. Ltd.*, 533 F.3d 1353, 1356 (Fed. Cir. 2008) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)). The first three factors comprise the so-called *prima facie* case of obviousness. *Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1350 (Fed. Cir. 2000).

678. The obviousness analysis requires an examination of the subject matter as a whole to ascertain if the claimed invention would have been obvious at the time that invention was made. 35 U.S.C. § 103; *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 401, 406 (2007). To the extent the claimed invention contains elements described in the prior art, the patent challenger must "identify[] 'a reason that would have prompted a person of ordinary skill in the

relevant field to combine the elements in the way the claimed new invention does'." *Takeda Chem. Indus, Ltd.. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (quoting *KSR Int'l Co.*, 550 U.S. at 401). "Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound." *Id.* at 1357. This is the best protection against the subtle but powerful attraction of a hindsight-based obviousness analysis. *See Amgen Inc. v. F. Hoffmann-La Roche, Ltd.*, 580 F.3d 1340, 1363 (Fed. Cir. 2009).

679. As the Federal Circuit Court of Appeals has recently reiterated, the danger of improper hindsight is most visible when the patent challenger selects claim elements from the prior art without providing any reason that the person of ordinary skill in the art would combine them at all, let alone in the manner recited by the claim. *In re NTP, Inc.*, No. 2010-1243, 2011 U.S. App. LEXIS 15814, at *39-40 (Fed. Cir. Aug. 1, 2011). "Care must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.'" *Id.* at *39-40 (quoting *Grain Processing Corp. v. American-Maize Prods. Co.*, 840 F.2d 902, 907 (Fed. Cir. 1988)).

680. Where the prior art discredits, disparages or somehow leads a person of skill in the art away from the claimed invention, that prior art is said to "teach away" from the invention and, thus, establish nonobviousness. *E.g.*, *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed, Cir. 2009); *Spectralytics, Inc. v. Cordis Corp.*, No. 2009-1564, 2011 WL 2307402, at *4-5 (Fed. Cir. June 13, 2011). What a reference teaches, and whether it teaches toward or away from the claimed invention, is a question of fact addressed to a person of

skill in the art. *Spectralytics, Inc. v. Cordis Corp.*, 2011 U.S. App. LEXIS 11981, at *15.

681. If a *prima facie* case of obviousness has been demonstrated, the patentee may offer evidence of secondary considerations of nonobviousness to rebut that showing. *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Contractors USA, Inc.*, 617 F.3d 1296, 1305 (Fed. Cir. 2010). Such evidence, when present, must be considered and includes the extent of commercial success of the patented invention, unexpected properties of the invention, whether the invention satisfies a long-felt need, whether others have failed to find a solution to a problem addressed by the patent, and any copying of the invention by others. *See Transocean Offshore Deepwater Drilling, Inc.*, 617 F.3d at 1304-5; *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1380 (Fed. Cir. 2006). The ultimate burden of proof on obviousness is always with the patent challenger and "never shifts." *See Tech. Licensing Corp. v. Videotek. Inc.*, 545 F.3d 1316, 1329 (Fed. Cir. 2008).

B. Findings of Fact

(i) Scope and Content of Prior Art Regarding Copolymer-1 and the Molecular Weight Characteristics of Copolymer-1

682. As described above in paragraphs 134-140, Professor Ruth Arnon and her colleagues at the Weizmann Institute discovered copolymer-1 in the 1960s, and first published their research on copolymer-1 in the 1971 Teitelbaum article. Because copolymer-1 was modeled after myelin basic protein, Pros. Arnon and her colleagues aimed for an average molecular weight of about 23,000 daltons. July Tr. (Arnon) 309:21-311:8. The 1971 Teitelbaum article described copolymer-1 as having an average molecular weight of 23,000 daltons. (July Tr. (Arnon) 311:24-312:22; PTX 499 at 242.)

683. In September 1974, Professor Arnon and her colleagues at the Weizmann Institute published an abstract reporting that copolymer-1 had been found to suppress EAE, a biological

model for MS. (PTX 509 at 1172.) The abstract states that copolymer-1 has a molecular weight of 23,000 daltons. (PTX 509 at 1172.) The abstract further reports that copolymer-1 compositions with molecular weights lower than 17,000 daltons or higher than 50,000 daltons "proved ineffective for the treatment of EAE." (July Tr. (Arnon) 312:23-313:18; Sept. Tr. (Grant) 1442:8-1444:9; PTX 509 at 1172-1173.)

684. The '550 patent, which issued to Yeda on November 19, 1974, describes compositions of several copolymers, including copolymer-1. The '550 patent states that the disclosed copolymers generally have a molecular weight "in excess of 10,000, and preferably above about 18,000" daltons. (Sept. Tr. (Grant) 1435:4-1437:19; Sept. Tr. (Zeiger) 839:18-840:18; PTX 26, col. 1:57-68.)

685. The only specific disclosure of copolymer-1 in the specification of the '550 patent appears in column 2, lines 19-30 of the patent specification. (Sept. Tr. (Grant) 1435:4-1437:19; Sept. Tr. (Zeiger) 933:14-934:18; PTX 26, col. 2:19-30.) There, the '550 patent describes a preferred copolymer, which is copolymer-1, having "a molecular weight of about 20,000 to 25,000" daltons. (Sept. Tr. (Grant) 1436:17-1437:9; Sept. Tr. (Zeiger) 933:21-934:4; PTX 26, col. 2:19-30.)

686. All of the claims of the '550 patent are directed to copolymers, including copolymer-1, having a molecular weight of 15,000 to 25,000 daltons. (Sept. Tr. (Grant) 1437:10-19; Sept. Tr. (Zeiger) 840:25-841:6; PTX 962 (B. Rao 6/9/2010 Dep.) at 103:5-105:13, 196:10-197:10, 198:9-199:12; PTX 26, col. 3:24 – col. 4:23; PTX 320 at MYL0000616.)

687. The '550 patent does not state how the average molecular weights reported in the patent were determined or the methodology used to generate the measurement. (Sept. Tr. (Grant) 1434:13-16, 1438:2-7; Sept. Tr. (Zeiger) 939:6-19, 956:10-957:13, 958:23-959:3.) The

'550 patent contains no disclosure, teaching or data regarding the molecular weight distribution or molar fractions of any copolymer. (Sept. Tr. (Grant) 1434:13-16, 1438:16-19; 1439:7-24, 1441:1-25; Sept. Tr. (Zeiger) 956:10-18, 957:2-6; PTX 26; PTX 320 at MYL0000616.)

688. During the prosecution of the '808 patent, the examiner rejected then-pending claims 17-20 as *prima facie* obvious in view of the '550 patent. (*See* PTX 13 at TEV000304138-144.) The applicants were able to overcome the obviousness rejection over the '550 patent by arguing that the '550 patent did not raise a *prima facie* case of obviousness, *i.e.*, by pointing out to the examiner that the '550 patent did not teach or suggest the claimed invention. (PTX 13 at TEV000304151-152.) The applicants did not rely on secondary considerations or unexpected results to overcome the obviousness rejection based on the '550 patent. (*See* PTX 13 at TEV000304151-152, 162-167).

689. The examiners of each of the other eight patents-in-suit considered the '550 patent extensively during prosecution of the patents-in-suit. (*See, e.g.,* PTX 14 at TEV000309018; PTX 15 at TEV000309103; PTX 17 at TEV000304221; PTX 18 at TEV000310385; PTX 19 at TEV000304453; PTX 20 at TEV000304582; PTX 21 at TEV000308838.) After the prosecution of the '808 patent, there were no subsequent obviousness rejections raised based on the '550 patent. (*See* PTX 13-21.)

690. European Patent Application No. 0383620 ("the EP '620 Application"), filed by Repligen Corporation on February 16, 1990 and published on August 22, 1990, discloses a biological process for making genes encoding polypeptides involving the use of recombinant DNA technology. (Sept. Tr. (Grant) 1445:4-22, 1446:23-1447:14; Sept. Tr. (Zeiger) 972:15-20; DTX 1970, p. 11, ll. 32-34.) The process described in the EP '620 Application does not involve the chemical synthesis of N-carboxyanhydrides. (Sept. Tr. (Grant) 1445:4-22, 1446:23-1447:14;

Sept. Tr. (Zeiger) 972:15-20; DTX 1970, p. 2, ll. 50-55.)

691. The EP '620 Application states that the process described can be used to make individual polypeptides that are "similar to" copolymer-1. (Sept. Tr. (Zeiger) 884:23-885:4, 972:15-20; DTX 1970, p. 2, l. 50.) These individual polypeptides are not mixtures like copolymer-1, and thus they do not have average molecular weights. Instead, each individual polypeptide disclosed has a discrete molecular weight. (Sept. Tr. (Grant) 1445:8-1446:4, 1446:23-1448:16; Sept. Tr. (Zeiger) 975:9-23, 976:15-23, 977:17-978:3; DTX 1970, p. 2, ll. 50-55, p. 11, ll. 32-34.)

692. The EP '620 Application discloses that the molecular weight of each individual polypeptide could be in the range of 5,000 to 50,000 daltons, but the reference focuses on individual polypeptides with sizes between 15,000 and 23,000 daltons because "COP-1 polypeptides within this range were previously tested in chemical trials." (Sept. Tr. (Grant) 1448:20-1449:19; Sept. Tr. (Zeiger) 977:8-978:3; DTX 1970, p. 5, 1l. 28-33.) Thus, the reference to 5,000 and 50,000 daltons in the EP '620 Application are references to individual molecular weights, not average molecular weights. (Sept. Tr. (Zeiger) 975:14-976:23.) The EP '620 Application does not disclose any copolymers having an "average molecular weight" of 5,000 daltons. (Sept. Trial (Grant) 1447:15-1448:10; Sept. Trial (Zeiger) 977:17-20.) Further, the EP '620 Application does not disclose measuring the average molecular weight of any copolymer using size exclusion chromatography, *i.e.*, using an appropriately calibrated suitable gel filtration column. (Sept. Trial (Grant) 1448:11-13; Sept. Trial (Zeiger) 976:15-23.)

693. The EP '620 Application contains no disclosure or teaching regarding a molecular weight distribution or molar fractions of copolymer-1. (Sept. Tr. (Grant) at 1448:17-19; *see generally* DTX 1970.)

694. The examiners of all nine patents-in-suit also considered the EP '620 Application. (*See e.g.,* PTX 13 at TEV000304110; PTX 14 at TEV000309018; PTX 15 at TEV000309103; PTX 17 at TEV000304221; PTX 18 at TEV000310385; PTX 19 at TEV000304453; PTX 20 at TEV000304582; PTX 21 at TEV000308838.) During prosecution of the patents-in-suit, the applicants were able to overcome any obviousness rejections based on the EP '620 Application for any allowed claims without relying on evidence of unexpected results, and the examiners of the patents-in-suit never cited unexpected results as the sole reason for allowing any claim over the EP '620 Application.

695. The precise reason for copolymer-1's biological activity remains unknown. (Sept. Tr. (Lisak) 118:3-8.) Whether certain portions of copolymer-1 or certain peptides found within copolymer-1 are responsible for its therapeutic properties also is not known. (DTX 1970 at 2:25.) Copolymer-1 batches with molecular weight distributions that overlap do not necessarily have the same function or activity in biological assays. (Sept. Tr. (Grant) 1460:14-1462:5, DTX 1762 at TEV003017837.)

696. Dr. Zeiger testified regarding the obviousness of the copolymer-1 molecular weight characteristics claimed in the patents-in-suit. Dr. Zeiger admitted, however, that he has never measured the molecular weight of a copolymer using SEC. (Sept. Tr. (Zeiger) 928:25-929:2.) In that same vein, Dr. Zeiger testified that he is aware that the Court has construed "average molecular weight" to mean "peak molecular weight detected using an appropriately calibrated suitable gel filtration column." (Sept. Tr. (Zeiger) 940:15-23.) But Dr. Zeiger testified that he does not hold himself out as an expert in SEC with respect to the use of molecular weight calibrants. (Sept. Tr. (Zeiger) 929:20-25.)

697. Dr. Zeiger likewise offered testimony regarding the obviousness of the claim limitations directed to the molecular weight distribution of copolymer-1, *i.e.*, the molar fraction claim limitations. But at his deposition, Dr. Zeiger could not recall ever generating a molecular weight distribution curve. (Sept. Tr. (Zeiger) 929:3-11, 953:6-11.)

698. Dr. Zeiger's opinions on these issues are entitled to little weight. Dr. Zeiger has never done any research regarding the fundamental underpinnings of SEC (Sept. Tr. (Zeiger) 929:15-17), and was not, in fact, proffered by the Defendants as an expert in SEC (Sept. Tr. (Zeiger) 798:4-800:16.).

699. Dr. Zeiger also offered the opinion that the claims directed to the treatment of multiple sclerosis (*e.g.*, claim 23 of the '539 patent) would have been obvious over the prior art. (PTX 8.) The Court should not credit these opinions, as Dr. Zeiger is not qualified to offer them. Dr. Zeiger admitted that he is not a medical doctor and that he has no experience treating people with multiple sclerosis. (Sept. Tr. (Zeiger) 966:7-16.) Despite his expertise being in biochemistry and polymer chemistry, Dr. Zeiger testified that he is confident that it would have been obvious to treat people with a new copolymer-1 composition. (Sept. Tr. (Zeiger) 967:16-22.)

(ii) Scope and Content of Prior Art Regarding Debenzylation Using HBr/acetic Acid

700. The patentees discovered and described in the patents-in-suit that the HBr in acetic acid used during the debenzylation stage in the process for making copolymer-1 would cleave the polypeptides formed during polymerization and, thus, could also be used to control the average molecular weight of the resulting copolymer-1. (Sept.Tr. (Sampson) 1641:8-23.) The patentees also discovered that by varying the time and temperature of the debenzylation reaction using HBr in acetic acid, a copolymer-1 composition with a predetermined molecular weight

profile, such as 7,000 daltons, could be synthesized. (Sept. Tr. (Sampson) 1641:18-1642:8; PTX 1, col. 4:48-col. 6:3.) Defendants have failed to show that these discoveries would have been obvious.

701. As Dr. Sampson testified, a person of skill in the art would not have been motivated to use HBr in acetic acid to cleave the peptide bonds in copolymer-1 polypeptides in order to control the molecular weight of a copolymer-1 sample. On the contrary, the prior art as a whole taught that peptide bonds would not be cleaved during exposure to HBr/acetic acid. (Sept. Tr. (Sampson) 1642:9-1643:6, 1646:22-1647:10, 1689:22-1690:11.)

702. As Dr. Sampson explained, HBr/acetic acid was a standard deprotecting agent used during the *synthesis* of polypeptides. In those cases, cleavage of the polypeptide chain would need to be minimized or avoided altogether. One of ordinary skill attempting to make polypeptides would not have been motivated to use a reagent that would *break* polypeptides. (Sept. Tr. (Sampson) 1642:9-1643:6, 1646:22-1647:10, 1655:13-1656:4; PTX 488.)

703. Dr. Sampson explained that of all the prior art refernces discussed at trial, only three directly investigated whether peptide bond cleavage occurred as a result of the use of HBr/acetic acid. Each of these references concluded that no cleavage had occurred. (Sept. Trial Tr. (Sampson) 1650:7-1651:9.)

704. A 1963 paper by nobel laureate Bruce Merrifield, "Solid Phase Peptide Synthesis. I. The Synthesis of a Tetrapeptide," *J. Am. Chem. Soc.*, 85: 2149-54 (1963) ("Merrifield 1963") (PTX 488), one of the most widely cited papers in peptide chemistry, taught that peptide bond cleavage would not occur upon exposure to HBr/acetic acid. (Sept. Trial Tr. (Sampson) 1644:10-1647:10; PTX 488.) Significantly, Dr. Merrifield specifically investigated whether peptide cleavage had taken place after treatment with HBr/acetic acid for 18 hours at 25°C,

conditions similar to those described in the patents-in-suit. He found no cleavage. (Sept. Trial Tr. (Sampson) 1644:20-1647:10; PTX 488 at 2151, 2153.)

705. Similarly, Yaron & Berger, "Multi-Chain Polyamino Acids Containing Glutamic Acid, Aspartic Acid and Proline,"*Biochimica et Biophysica Acta*, 107: 307-332 (1965) ("Yaron & Berger 1965") (DTX 1934) reported that no cleavage of peptide bonds was detected when HB/acetic acid was used for debenzylation carried out at 2 degrees for 3 days. (Sept. Trial Tr. (Sampson) 1650:7-1651:9; Sept. Trial Tr. (Zeiger) 851:9-853:3; 1685:13-22; PTX 1934.) The authors reported that under those conditions, they were able to obtain 100 percent deprotection of benzyl groups and avoid peptide bond cleavage. (Sept. Trial Tr. (Sampson) 1650:7-1651:9; 1685:13-22; Sept. Trial Tr. (Zeiger) 851:9-853:20; PTX 1934.)

706. Yaron and Berger, "Multichain Polyamino Acids of Well Defined Degrees of Polymerization, *Bulletin of the Research Counsel of Israel: Section A, Chemistry*, 7A(2):96-97 (1958) ("Yaron & Berger 1958") (DTX 3233) also investigated whether peptide bond cleavage occurred when HBr in acetic acid was used to deprotect benzyl groups during the synthesis of copolymers. The authors concluded that "no degradation in the side chains occurred during debenzylation with HBr in glacial acetic acid at 2 degrees for three days." (Sept. Trial Tr. (Sampson) 1650:7-1651:9; Sept. Trial Tr. (Laird) 1146:9-1147:6.) As Dr. Sampson explained, this meant that no peptide bonds had been cleaved even after three days of exposure to HBr/acetic acid.

707. According to both Dr. Sampson and Sandoz's expert Dr. Laird, the time and temperature of 2 degrees for three days reported in Yaron and Berger 1958 would be equivalent, through the application of a well-known chemical rule of thumb to about 22-25 degrees for about 17-18 hours, conditions similar to those reported in the patents-in-suit. (Sept. Trial Tr. (Laird)

1146:9-1147:6; Sept. Trial Tr. (Sampson) 1650:7-1651:9, 1685:13-1686:18; PTX 1934 at 318; PTX 3233 at 97.) Since *no cleavage* was observed in the conditions used in Yaron and Berger 1958, one of ordinary skill in the art in 1994 would similarly expect that use of HBr in acetic acid for 17 hours at 25°C, as described in Example 4 of the patents-in-suit, would likewise result in *no cleavage* of peptide bonds. (Sept. Trial Tr. (Sampson) 1685:13-1686:18; DTX 1934 at 318.)

708. The other prior art refernces discussed by Drs. Zeiger and Laird would not teach the person of ordinary skill to use HBr/acetic acid to cleave peptide bonds.

709. The two prior art references that mention the use of HBr/acetic acid during the synthesis of copolymer-1, the ’550 patent and the 1971 Teitelbaum article, describe using HBr/acetic acid only for the purpose of debenzylation – *i.e.*, removing the benzyl protecting group from the glutamic acid in protected copolymer-1. (Sept. Trial Tr. (Sampson) 1651:20-1652:11, 1653:4-1655:12; PTX 26, col. 2:53-64; PTX 499 at 243.) Neither of these references mention peptide bond cleavage during the debenzylation step, nor do they mention the use of HBr in acetic acid to control the molecular weight of the resulting copolymer-1 product. (Sept. Trial Tr. (Sampson) 1651:20-1652:11, 1653:4-1655:12; PTX 26; PTX 499.)

710. Dr. Sampson testified that a person of ordinary skill in the art would have understood that the Weizmann scientists controlled molecular weight by adjusting the ratio of initiator to N-carboxyanhydrides of the respective amino acids during polymerization. (Sept. Trial Tr. (Sampson) 1652:12-1656:4; PTX 499; DTX 1783.)

711. Two of the prior art references relied on by the Defendants – the Katchalski & Sela reference and the Hayashi reference – discuss the use of HBr for debenzylation purposes in compounds other than copolymer-1, but they contain no independent or original observations

concerning peptide bond cleavage. These references simply report discussion of suspected bond cleavage from earlier literature (Sept. Trial Tr. (Sampson) 1647:11-1648:10), and neither mentions the use of HBr/acetic acid to control molecular weight. (*See* Sept. Trial (Sampson) 1647:25-1648:10, 1653:10-1655:8; Sept. Trial (Zeiger) 820:17-821:4; DTX 1781; DTX 1783.) Moreover, Hayashi 1985 does not even discuss the use of HBr in acetic acid. (Sept. Trial (Laird) 1150:16-1151:12; DTX 1781 at 464.)

712. Four other prior art references relied on by the Defendants discuss possible peptide bond cleavage based upon an observed change in the molecular weight of a peptide after the use of HBr. These references, however, contain no direct observation or testing to determine whether, in fact, peptide bond cleavage had occurred and whether HBr was responsible for such cleavage. (*See* Sept. Trial Tr. (Sampson) 1648:11-1650:6; DTX 1855; DTX 3327; DTX 1784.)

713. As Dr. Sampson testified, it is also significant that the references Defendants' experts rely that suggest possible peptide bond cleavage all pre-date the Merrifield article. A person of skill in the art in 1994 looking at the literature as a whole, including the Merrifield article, would not have understood that HBr in acetic acid would cleave peptide bonds. The person of ordinary skill in the art would therefore not have been motivated to use that reagent in order to control the molecular weight of copolymer-1. (Sept. Trial Tr. (Sampson) 1655:13-1656:17.)

714. This finding is supported by the fact that Defendants' experts could not point to a single literature reference in all the years prior to 1994 that actually used HBr/acetic acid to control the molecualr weight of a polypeptide. (Sept. Tr. (Sampson) 1689:22-1690:11.)

(iii) Facts Relating to Secondary Conditions Support a Finding of Nonobviousness

715. MS was first recognized as a distinct disease in the 1860s. (Sept. Tr. (Lisak)

88:8-89:18.) Yet by the early 1990s, despite repeated attempts by multiple entities, no effective treatment had been developed that could slow the progress of the disease. (Sept. Tr. (Lisak) 102:2-9, 131:14-136:19; PTX 523; PTX 538; PTX 565; PTX 591.) In 1994, the only disease-modifying treatment available for MS was Betaseron®, an interferon treatment that is ineffective in about 40% of MS patients and that causes significant side effects, including liver and bone marrow problems, depression, and a flu-like syndrome. (Sept. Tr. (Lisak) 125:25-126:3, 103:3-104:2, 104:11-105:18.) Thus, in 1994, there remained unmet needs for (1) another effective treatment for RRMS patients; (2) a RRMS treatment that worked differently than an interferon treatment; and (3) an effective treatment that was more tolerable and caused less side effects than an interferon treatment. (Sept. Tr. (Lisak) 126:10-127:18; Sept. Tr. (Green) 1392:11-1393:20.)

716. The introduction of Copaxone® in 1997 fulfilled all of these needs. (Sept. Tr. (Lisak) 127:15-130:25; PTX 667; PTX 671. Copaxone® works differently than interferons and is thus able to effectively treat many of the patients for whom interferons are ineffective. (Sept. Tr. (Lisak) 103:3-104:2, 118:9-119:7; 127:15-130:25; PTX 667, PTX 671.) Copaxone® also does not cause many of the significant side effects associated with interferon therapy. Sept. Tr. (Lisak) 117:1-15. With Copaxone®, physicians were able to provide an effective treatment option for patients that did not respond to the interferons, and that did not cause the significant side effects associated with interferon treatment. (Sept. Tr. (Lisak) 126:12-127:20.) While Mylan's clinician expert, Dr. Green, opined that the higher molecular weight copolymer-1 studied by Dr. Bornstein in the 1980s would have satisfied these needs if it had been approved, this speculative testimony is not reliable given that Dr. Green was not even practicing medicine until 2001—well after the time period relevant to this secondary consideration. (Sept. Tr. (Green) 1364:19-24; 1380:3-19.)

717. Dr. Lisak explained that his prescriptions for Copaxone® have increased over time because of the clinical advantages of the product over the competing treatments. (Sept. Tr. (Lisak) 119:8-120:9.) Dr. Lisak's testimony is consistent with the observation of Teva's corporate representative, Mr. Jon Congleton that as physicians gained experience prescribing Copaxone®, "they saw the benefit that their patients were deriving" and "[a]s that knowledge accumulated, that experience accumulated, the utilization of Copaxone grew." (Sept. Tr. (Congleton) 50:12-51:2.)

718. The undisputed facts demonstrate that Copaxone®, Teva's copolymer-1 treatment for RRMS, has been a substantial commercial success. Annual sales of Copaxone® have grown nearly 100-fold from $25 million in 1997 to approximately $2.25 billion in 2010. (Sept. Tr. (Congleton) 49:8-12, 59:18-20.) Sales of Copaxone® in the United States have steadily grown and overtaken sales of its interferon competitors during this time and it has become the treatment of choice for RRMS by nearly a factor of two. (Sept. Tr. (Congleton) 50:12-51:2.) Since its introduction, total sales for Copaxone® have exceeded $10 billion, despite constant pressure from competitors. (Sept. Tr. (Congleton) 59:21-23, 66:6-7.) Approximately 100,000 patients are currently using Copaxone® to treat their multiple sclerosis. (Sept. Tr. (Congleton) 51:19-22.)

719. Natco and Mylan also represented in their ANDA submission to the FDA that Copaxone® is the "first choice of drug for remitting relapsing form of multiple sclerosis." (PTX 320 at MYL0000615.) "When compared to other disease[] modifying drugs . . ., glatiramer acetate has fewer side effects. It is also [the] drug of choice for patients of multiple sclerosis to be shifted from Interferon beta 1a and 1b due to adverse reactions and intolerance." (PTX 320 at MYL0000615; *see also* PTX 963 (B. Rao 9/30/2010 Dep.) at 226:23-228:13 (testifying that Copaxone® has "a better side-effect profile" and "a better therapeutic efficacy profile" as

compared to the interferon treatments).)

720. The evidence at trial demonstrated that Copaxone® and Teva's process for manufacturing Copaxone® are covered by at least one claim of each of the patents-in-suit. (Sept. Tr. (Gokel) 1589:13-1590:20.) Dr. Gokel testified at trial that Copaxone® meets the "copolymer-1" term, as it has been construed by the Court. (Sept. Tr. (Gokel) 1588:15-1589:12, 530:25-531:25.) Dr. Gokel further explained that Teva uses the same process steps that are in the patents-in-suit to make Copaxone®. (Sept. Tr. (Gokel) 1584:9-1590:20.)

721. Dr. Grant testified that based on the data he had seen from Copaxone® certificates analysis and calculations based on data provided by Sandoz and Mylan that Copaxone® meets the average molecular weight, copolymer-1 molar fraction and TFA-copolymer-1 limitations of the asserted claims. (PTX 105, PTX 349 at SDZ00017948-949; PTX 392 ; PTX 990 at "Copolymer-1 Molar Fraction Limitations-Copaxone" and "TFA Copolymer-1 Molar Fraction Values-Copaxone"; Sept. Tr. (Grant) 1468:5-1477:15.)

722. Dr. Lisak's testimony at trial also demonstrates that Copaxone® meets the limitations related to treatment of multiple sclerosis. (Sept. Tr. (Lisak) 137:4-147:22; Sept. Tr. (Gokel) 1589; PTX 206; PTX 697; PTX 734.)

723. The evidence at trial also established that Copaxone® is covered by at least one claim of each of the patents-in-suit. Dr. Grant, testified that Copaxone® meets the average molecular weight and molar fraction limitations of each claim of the patents-in-suit. (Sept. Tr. (Grant) 1476:25-1477:15.) Dr. Gokel also testified that at least one claim of each patent-in-suit covers Copaxone®. (Sept. Tr. (Gokel) 531:4-25, 1584:9-1590:20.)

724. The success of Copaxone® has occurred in a difficult drug development environment. Since the 1860s, numerous attempts to develop an effective treatment for MS have

failed. (Sept. Tr. (Lisak) 131:14-132:7.) Despite showing some promise, these treatments have failed to either benefit the patient, were toxic or not tolerated, and in some cases, actually worsened the disease. (Sept. Tr. (Lisak) 131:14-136:19.)

725. At trial, Dr. Lisak described some of the more recent failed attempts to develop MS treatments. Isoprinisone and prednisone were both tested in the early 1980s and found not to provide any benefit in slowing the progression of the disease. (PTX 523; Sept. Tr. (Lisak) 132:18-24.) Transfer factors, obtained from the white blood cells of healthy individuals, were also studied but found not to provide any benefit to MS patients. (Sept. Tr. (Lisak) 132:18-24; PTX 538.)

726. Various immunosuppressants have also failed as effective treatments for MS. Trials on Roquinimex were cut short due to the discovery of significant side effects, including heart attacks and even deaths in some patients. (Sept. Tr. (Lisak) 132:25-133:4; PTX 627.) Gusperimus failed to provide any benefit to patients. (Sept. Tr. (Lisak) 133:5-7; PTX 591.) Sulfasalazine failed to show any therapeutic benefit after three years of patient use, even though the drug initially looked promising after a year of use. (Sept. Tr. (Lisak) 133:7-12; PTX 617.) Cladribine is a chemotherapy drug that turned out to have unacceptable toxicity for use in treating MS. (Sept. Tr. (Lisak) 133:15-21; PTX 644.)

727. Lenercept, a cytokine modulator used to treat rheumatoid arthritis, was tested for efficacy in treating MS and not only failed to provide any benefit, some patients endured more attacks of MS symptoms and developed more active lesions. (Sept. Tr. (Lisak) 133:23-134:6; PTX 623.) Infliximab, another cytokine modulator, was also ineffective in treating MS and worsened the condition of some patients. (Sept. Tr. (Lisak) 134:7-10; PTX 605.) TGF-β2 is a cytokine that was shown to provide no therapeutic benefits in clinical trials. (Sept. Tr. (Lisak)

134:11-14; PTX 616.)

728. Several antigen-derived therapies have also failed as effective treatments for MS. Patients who received oral bovine myelin in Phase III clinical studies fared no better than patients on placebo. (Sept. Tr. (Lisak) 134:15-21; PTX 644.) Tiplimotide, another antigen therapy, actually worsened the condition of some patients. (Sept. Tr. (Lisak) 134:22-25; PTX 626.)

729. Despite some promise, various monoclonal antibodies have also failed as treatments for MS. Muromonab-CD3 is a monoclonal antibody that cause significant toxicity in patients. (Sept. Tr. (Lisak) 135:3-8; PTX 565.) Priliximab was found to be ineffective in a Phase II clinical study. (Sept. Tr. (Lisak) 135:3-8; PTX 644.) Development of Antova for treatment of autoimmune diseases, including MS, stopped after patients began developing blood clots and deep vein thrombosis. (Sept. Tr. (Lisak) 135:9-13; PTX 99.)

730. As referenced above in paragraphs 165-69, the record also reflects that the lower molecular weight copolymer-1 developed by the inventors achieved unexpected results, including reduced toxicity. Further, the record shows that both defendants copied the synthetic process for making copolymer-1 claimed in the patents-in-suit. *See* Paragraphs 288-300, 252-257.

C. Conclusions of Law

(i) Copolymer-1 Compositions Having the Claimed Average Molecular Weight Characteristics Were Not Obvious.

731. Defendants rely on two pieces of prior art in support of their contention that the claimed copolymer-1 compositions would have been obvious to the person of ordinary skill in the art: U.S. Patent 3,849,550 ("the '550 patent") and the EP '620 Application ("EP '620 Application"). As set forth above, the PTO considered both the '550 patent and the EP '620

Application during the prosecution of each of the nine patents-in-suit. Therefore, Defendants face a heavy burden of proving invalidity. *In re Omeprazole Patent Litigation*, 490 F. Supp. 2d at 500 (citing *Am. Hoist & Derrick Co. v. Sowa & Sons*, 725 F.2d 1350, 1358-60 (Fed. Cir. 1984)); *see also Tokai Corp.*, 632 F.3d at 1367.

732. Neither the '550 patent nor the EP '620 Application, alone, in combination, or in view of the knowledge of the person of ordinary skill in the art renders obvious copolymer-1 compositions with the claimed average molecular weight ranges.

733. The '550 patent does not disclose a copolymer-1 composition having an average molecular weight of about 5,000 to 9,000 daltons or within any of the other claimed molecular weight ranges, nor does it suggest such a composition. (Sept. Tr. (Zeiger) 841:19-842:13.) Indeed, Mylan's expert, Dr. Zeiger, admitted that the '550 patent teaches that the preferred molecular weight range for the copolymers it discloses is above 18,000 daltons. (Sept. Tr. (Zeiger) 840:16-18, 843:1-3.) Like the '550 patent, the EP '620 Application does not disclose copolymer-1 compositions with an average molecular weight of about 5,000 to about 9,000 daltons. Indeed, the EP '620 Application is not even directed to copolymer-1 compositions, as the term "copolymer-1" has been interpreted by the Court. (Sept. Tr. (Grant) 1445:4--1447:-14; Sept. Tr. (Zeiger) 972:15-20; DTX 1970, p. 2, ll. 50-55, p. 11, 1.32-1.34.) Instead, the EP '620 Application is directed to discrete polypeptides made through recombinant DNA technology and identifes a preferred molecular weight for these individual polypeptides of 15,000 to 23,000 daltons. (Sept. Tr. (Grant) 1448:20-1449:19; Sept. Tr. (Zeiger) 972:15-20, 977:8-978:3; DTX 1970, p. 5, 1l. 28-33.)

734. Defendants have offered no reason why, based on the prior art, the person of ordinary skill in the art would have been motivated to make a copolymer-1 composition with a

peak average molecular weight of about 5,000 to 9,000 daltons. *Takeda Chem. Indus.*, 492 F.3d at 1350 ("[i]t remains necessary to identify some reason that would have lead a chemist to modify a known compound in a particular manner to established prima facie obviousness of a new claimed compound"). Nothing in the prior art suggests any reason that a person of ordinary skill would change, adjust or lower the average molecular weight of copolymer-1 to the claimed ranges. Based on the teachings of the '550 patent and the EP '620 Application, the person of ordinary skill in the art would have no reason to select or to make a copolymer-1 composition in the specific average molecular weight range of about 5 to 9 kilodaltons, or within the ranges of "about 4 to about 9 kilodaltons," or 6.25-8.4 kilodaltons.

735. In fact, the prior art would have taught the person of ordinary skill *away* from making a copolymer-1 composition with an average molecular weight of about 5,000 to about 9,000 daltons. Both the '550 patent and the EP '620 Application express a preference for compositions with molecular weights above 15,000, and more preferably between 20,000 and 25,000 daltons. (Sept. Tr. (Grant) 1437:10-19; 1448:20-1449:19; Sept. Tr. (Zeiger) 933:21-934:4, 977:8-978:3; PTX 26, col. 3:24-col. 4:3; DTX 1970, p. 5, 1l. 28-33.) By teaching that higher average molecular weights were preferred, these references teach away from the claimed lower average molecular weight copolymer-1 compositions. *See e.g.*, *Takeda Chem. Indus.*, 492 F.3d at 1357-58; *In re Baird*, 16 F.3d 380, 382-83 (Fed. Cir. 1994).

736. This is entirely consistent with the teaching of other available prior art, like the 1974 Teitelbaum reference, which expressly teaches away from copolymer-1 with an average molecular weight below 17,000 daltons, identifying such a composition as "ineffective" for the treatment of EAE." (July Tr. (Arnon) 312:23-313:18; Sept. Tr. (Grant) 1442:8-1444:9; PTX 509 at 1172-1173.)

737. Apparently acknowledging that they have provided no evidence as to why a person of ordinary skill in the art would have lowered the average molecular weight of copolymer-1 based upon the prior art, Defendants argued at trial that *prima facie* obviousness can be established based solely on what they describe as overlapping or abutting molecular weight ranges between the copolymer-1 compositions of the prior art and the claimed copolymer-1 compositions. Defendants' argument does not hold up when applied to the case law concerning overlapping or abutting ranges.

738. First, there is no overlapping or abutting range with respect to the claimed "average molecular weight." Even if the '550 patent taught a copolymer-1 composition having an "average molecular weight," *i.e.*, a peak molecular weight detected using an appropriately calibrated suitable gel filtration column, of 10,000 daltons (which it does not), such a composition does not overlap with a peak average molecular weight range of "about 5 to 9 kilodaltons," "about 4 to about 9 kilodaltons" or "6.25-8.4 kilodaltons." (Sept. Tr. (Zeiger) 938:11-15; 941:8-16.)

739. Nor does the peak average molecular weight of "about 9 kilodaltons" "abut" an average molecular weight of 10,000 daltons. In order to abut, prior art and claimed ranges must literally touch. *See e.g., In re Woodruff*, 919 F.2d 1575, 1576, 1578 (disclosed range of "about 5%" abutted claimed range of "more than 5%"); *In re Malagari*, 499 F.2d 1297, 1298, 1303 (CCPA 1974) (disclosed range of 0.03 and 0.07% carbon abutted range of 0.02-0.03%). Here, the '550 patent does not disclose how the molecular weights of the disclosed copolymers were measured, but even if it discloses a peak average molecular weight of 10 kilodaltons, the "average molecular weight" ranges of the claims and the '550 patent do not touch. Nor can an overlapping or "abutting" range case be made out with regard to the EP '620 Application, which

discloses neither copolymer-1 nor an average molecular weight for copolymer-1. (Sept. Tr. (Grant) 1444:13-1448:16; Sept Tr. (Zeiger) 884:23-885:4, 972:15-20, 975:9-23, 976:15-23; DTX 1970, p.2, l. 50.)

740. Rather than address the invention as claimed, Defendants argue that because there must have been an overlap in the molecular weight of some of the species within the mixture of copolymer-1 batches alleged to be in the prior art with the distributions of the claimed invention, there is an overlap in the claimed ranges. This is incorrect as a matter of law and science. As a matter of law, the "overlapping range" cases refer to an overlap of ***claimed*** ranges. *See e.g.*, *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) ("A prima facie case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art.") Here, Defendants acknowledge that they have not demonstrated such an "overlap." (Sept. Tr. (Zeiger) 941:8-16.)

741. Moreover, defendants have *no* prior art to rely on to establish this alleged "overlap." Instead, at trial the Defendants relied on (1) an internal Teva document created after the May 24, 1994 patent filing date, which compares the molecular weight of batches of copolymer-1 used in Dr. Bornstein's clinical trial with a batch of copolymer-1 having an average molecular weight within the claimed range, and (2) Figure 2 of the patents-in-suit. None of this information, however, was part of the prior art in 1994 and, thus, it cannot be relied on to establish obviousness. *Riverwood Int'l Corp. v. R.A. Jones & Co.*, 324 F.3d 1346, 1354 (Fed. Cir. 2003); *Astra Aktiebolag v. Andrx Pharms.*, 222 F. Supp. 2d 423, 575-78 (S.D.N.Y. 2002), aff'd sub nom. *In re Omeprazole Patent Litig.*, 84 Fed. Appx. 76, 81 (Fed. Cir. 2003) (rejecting obviousness argument based on documents not available to public). Defendants' analysis is clearly based on impermissible hindsight. *See Amgen Inc.*, 580 F.3d at 1363.

742. Moreover, even if the claimed molecular weight ranges abutted the prior art, Defendants have failed to prove, as required, that a person of ordinary skill in the art would have had an expectation that a copolymer-1 composition within the claimed average molecular weight range would exhibit the same properties as the prior art high average molecular weight copolymer-1. *See Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 783 (Fed. Cir. 1985). To establish obviousness, Defendants need to prove by clear and convincing evidence that the person of ordinary skill in the art had a reasonable expectation of success in selecting the claimed molecular weight parameters to make an active copolymer-1 product. *See Genetics Inst. V. Novartis Vaccine & Diagnostics*, No. 2010-1264, 2011 WL 3672474, at *12 (Fed. Cir. Aug. 23, 2011) (despite the overlap in proteins, "the nontrivial differences in the proteins at issue compel the requirement of identifying a reason for the chemical modification"); *Takeda Chem. Indus.*, 492 F.3d ar 1360-61; *Key Pharms., Inc. v. Hercon Labs. Corp.*, 981 F. Supp. 299, 313 (D. Del. 1997), aff'd 161 F.3d 709 (Fed. Cir. 1998). Defendants have failed to do so.

743. As discussed above, Defendants attempt to rely on the fact that some percentage of copolymer-1 species in the prior art composition would be in the same molecular weight range as copolymer-1 species in the claimed compositions. But, as discussed above, defendants' arguments are based on documents and information not available to the public prior to May 24, 1994. There was nothing in the prior art disclosing or suggesting the overlap relied on by Defendants.[10]

744. Even if the person of ordinary skill in the art would have known the extent to which the prior art and claimed compositions would overlap, however, Defendants have offered no evidence that the person of ordinary skill in the art would have expected such compositions to

have the same or similar biological properties based solely on the degree of overlap in the compositions. *See Genetics Inst.*, 2011 WL 3672474, at *12-13. There was no evidence offered at trial demonstrating that the person of ordinary skill in the art would expect copolymer-1 compositions with overlapping molecular weight distributions would have similar biological properties. (Sept. Tr. (Zeiger) 966:3-967:22.) Indeed, the available evidence suggests just the opposite as the prior art taught that copolymer-1 compositions with lower average molecular weights would likely be ineffective. (July Tr. (Arnon) 312:23-313:18; Sept. Tr. (Grant) 1442:8-1444:9; PTX 509 at 1172-73.)

745. Defendants have failed to establish that a copolymer-1 composition with an average molecular weight of about 5,000 to 9,000 daltons, or any of the other claimed low average molecular weight ranges (*i.e.*, about 4 to about 9 kilodaltons and 6.25 to 8.4 kilodaltons) were *prima facie* obvious.

(ii) Copolymer-1 Compositions with the Claimed Molar Fraction Limitations Would Not Have Been Obvious

746. Defendants also contend that copolymer-1 compositions with the claimed molar fraction limitations would have been obvious. Specifically, Defendants contend a copolymer-1 composition with over 75% of its molar fraction within the molecular weight range from about 2 to about 20 kilodaltons, with less than 5% of its molar fraction above 40 kilodaltons, or not more than 2.5% of its molar fraction above 40 kilodaltons, would have been obvious to a person of ordinary skill in the art in May 24, 1994. Nothing in the prior art, however, suggested or taught the claimed molar fraction limitations. Defendants' argument is based on hindsight and unsupported speculation.

[10]Even if the figures relied on by Defendants had been available to the public, they do not demonstrate an overlap of "average moelcular weights," *i.e.*, peak molecular weights.

747. Neither the '550 patent nor the EP '620 Application disclose or suggest copolymer-1 with the specifically claimed molar fraction limitations. (Sept. Tr. (Grant) 1434:13-16, 1439:2-24, 1441:10-25, 1448:17-19; Sept. Tr. (Zeiger) 956:13-958:16.) Neither reference provides any disclosure of the percentage of molecules in any range on a molar fraction basis. (Sept. Tr. (Grant) 1434:13-16, 1439:2-24, 1441:10-25, 1448:17-19; Sept. Tr. (Zeiger) 956:13-958:16.) Neither reference teaches anything about the molecular weight distribution of any polypeptide mixture disclosed in the references. (Sept. Tr. (Grant) 1434:13-16, 1439:2-24, 1441:10-25, 1448:17-19; Sept. Tr. (Zeiger) 956:13-958:16.) Each of the relevant claims relate to a calculation of the molar fractions of copolymer-1, but there was no data presented in the prior art from which a molar fraction could be calculated. (Sept. Tr. (Grant) 1434:13-16, 1439:2-24, 1441:10-25, 1448:17-19; Sept. Tr. (Zeiger) 956:13-958:16.) Nor would a person of ordinary skill in the art have had any reason to make, based on the teachings of the prior art, a copolymer-1 composition with the claimed molar fraction characteristics. There was no evidence presented at trial showing that a person of ordinary skill in the art would have had a reason to focus on or even consider copolymer-1 having any particlar molar fraction characteristics.[11] *Takeda Chem. Indus.*, 492 F. 3d 1360-61. Defendants obviousness argument concerning the molar fraction limitations is based entirely on hindsight. *See Amgen, Inc.*, 580 F.3d at 1363.

748. Like the "average molecular weight" limitations, Defendants again attempt to focus on alleged "overlapping ranges" to support their argument regarding the obviousness of the asserted claims. Defendants argue, based on Figure 2 of the patents-in-suit and the Gad Report discussed above (DTX 1704), that batches prepared using the synthetic processes disclosed in the

[11] There was, similarly, no disclosure in the prior art of any information relating to the molar fraction of TFA-copolymer-1. (Sept. Tr. (Grant) 1441:22-25, 1448:17-19; Sept. Tr. (Zeiger) 956:19-957:13.)

'550 patent would necessarily have had a large portion of individual polypeptides within the claimed molar fraction ranges. (Sept. Tr. (Zeiger) 987:1-989:29.) First, Defendants point to nothing that supports the argument that batches made according to the prior art '550 method would necessarily meet the molar fraction limitations. And for the reasons set forth above, this argument is legally meritless. *Riverwood Int'l Corp.*, 324 F.3d at 1354; *Astra Aktiebolag*, 222 F. Supp. 2d at 575-78.

749. Because a person of ordinary skill in the art would not have found obvious a copolymer-1 having the claimed average molecular weight or molar fraction limitations, Defendants have failed to prove by clear and convincing evidence that the following claims are invalid for obviousness on that basis: claim 1 of the '808 patent, claim 1 of the '589 patent, claim 1 of the '847 patent, claims 1-3 of the '430 patent, claim 1 of the '476 patent, claim 1 of the '161 patent, claims 1 and 8 of the '898 patent, and claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent.

(iii) The Claimed Process for Making Copolymer-1 Was Not Obvious

750. Defendants also failed to establish that the process limitations in the patents-in-suit would have been obvious. Defendants failed to prove that the use of Hydrobromic (HBr) acid in acetic acid to cleave peptide bonds in order to control molecular weight would have been obvious to a person of ordinary skill in the art in May 1994. While it was known in the art that HBr in acetic acid could be used for debenzylation, a reaction to remove the benzyl protecting group from an amino acid, such as glutamic acid, there was no prior art disclosure that this reagent could also depolymerize polypeptides to control the average molecular weight.

751. As a preliminary matter, the Defendants have failed, as set forth above, to prove by clear and convincing evidence that a person of ordinary skill would have targeted the claimed average molecular weights or molecular weight molar fractions. Without establishing that a

person of ordinary skill would have sought to obtain copolymer-1 having these molecular weight characteristics, Defendants have provided no reason that a person of ordinary skill would have been motivated to research or even consider the use of HBr/acetic acid to cleave peptide bonds to control the average molecular weight or molar fraction characteristics of copolymer-1. There is no evidence that a person of ordinary skill in the art would have been motivated to search for some means to decrease the molecular weight of copolymer-1. Defendants' obviousness theory fails for at least this reason.

752. Defendants' have also failed to demonstrate by clear and convincing evidence that a person of ordinary skill would have understood at the time the patent application was filed in 1994 that HBr/acetic acid could have been used to cleave peptide bonds in order to control the molecular weight of copolymer-1.

753. The only two references that Drs. Zeiger and Laird introduced regarding the use of HBr in acetic acid for synthesizing copolymer-1 were the '550 patent and the Teitelbaum 1971 article. But neither of these references mention peptide cleavage during the debenzylation step, nor do they mention the use of HBr in acetic acid to control the molecular weight of the resulting copolymer-1 product. (Sept. Tr. (Sampson) 1651:20-1652:11, 1653:4-1655:12; PTX 26, col. 2 ll.53-64; PTX 499 at 243.)

754. The Defendants attempt to fill this gap in the prior art by relying on references from the 1950's and early 1960's, which suggest, according to Defendants, possible cleavage of peptide bonds following the use of HBr in acetic acid. (Sept. Tr. (Laird) 1139:10-1149:9; Sept. Tr. (Zeiger) 899:12-23, 951:23-15.) Dr. Zeiger, Mylan's expert, testified that the person of ordinary skill in the art would find these references by following a "trail" of six references, that begins with the work of the patentees as described in the '550 patent. (Sept. Tr. (Zeiger) 817:19-

818:17, 945:14-952:15.) But these references do not cure the deficiency in the defenandants' prior art case.

755. The evidence shows that a person of skill in the art would not have been motivated to use HBr in acetic acid to cleave the peptide bonds in copolymer-1 polypeptides in order to control the molecular weight of a copolymer-1 sample, even if one assumes that the person of skill were motivated to decrease the average molecular weight of copolymer-1.

756. HBr in acetic acid was used as a step in the *synthesis* of polypeptides, where the cleavage of the polypeptide chain would viewed negatively as something that would need to be minimized or avoided altogether. (Sept. Tr. (Sampson) 1642:9-1643:6, 1646:22-1647:10, 1655:13-1656:17, 1683:16-19; PTX 488.) The prior art relied on by defendants shows that the alleged cleavage disclosed was, at best, an undesirable side reaction, not something that would be viewed as a tool to be used to decrease the molecular weight of copolymer-1. (Sept. Tr. (Sampson) 1642:9-20, 1655:13-1656:4; Sept. Tr. (Laird) 1139:22-1140:8; 1154:2-1155:12.)

757. The opinions of Defendants' experts are based on hindsight. Dr. Laird and Dr. Zeiger cite to references reporting that the use of HBr in acetic acid for debenzylation could potentially result in some peptide cleavage. (Sept. Tr. (Laird) 1139:10-1142:9.) But neither Dr. Laird nor Dr. Zeiger offered any explaination why the person of ordinary skill in the art would seek to use the debenzylation reaction, or HBr in acetic acid, to cleave the peptides during the process for making copolymer-1. (Sept. Tr. (Laird) 1155:4-23; Sept. Tr. (Zeiger) 817:19-818:17, 945:14-952:15.)

758. Dr. Zeiger's testimony that the person of ordinary skill in the art would ignore the Merrifield 1963 article because it did not directly address whether HBr in acetic acid could cleave a specific type of peptide – a gamma-benzyl glutamic acid containing peptide – is not

credible. That testimony is directly refuted by the testimony of Dr. Laird that the person of ordinary skill in the art would not focus on benzyl containing peptide bonds because all peptide bonds are closely similar. (Sept. Tr. (Laird) 1151:18-25.) Moreover, Dr.. Zeiger's focus on gamma-benzyl glutamic acid containing peptides is based on hindsight. Dr. Zeiger did not provide any basis for the person of ordinary skill in the art to conclude that gamma-benzyl glutamic acid bonds is the site of cleavage in protected copolymer-1 polypeptides treated with HBr in acetic acid, nor did Dr. Zeiger identify any reason that a person of skill in the art would have focused on the gamma-benzyl glutamic acid bond other than the fact that it is found in copolymer-1.

759. Certain asserted claims of the patents-in-suit include specific time and temperature limitations. Those include claims 2 and3 of the '898 patent and claims 2 and 3 of the '430 patent. Defendants failed to prove that the person of ordinary skill in the art would have been motivated to select or would have selected any particular time and temperature for the HBr/acetic acid step or that the person of ordinary skill in the art would have had any expectation that selecting a particular time and temperature for performing the HBr in acetic acid deprotection reaction would affect the resulting average molecular weight or molar fractions of the copolymer-1 product. (Sept. Tr. (Sampson) 1644:20-1647:10; 1685:13-1686:18; PTX 488 at 2151, 2153; DTX 1934 at 318.) Thus, Defendants have failed to establish that the person of ordinary skill in the art would have selected a time of 10-50 hours and a temperature of 20-28 degrees C or a time of about 17 hours and a temperature of about 26 degrees C for the reaction of protected copolymer-1 with HBr in acetic acid, as recited in claims claims 2 and 3 of the '898 patent and claims 2 and 3 of the '430 patent. Defendants have failed to demonstrate the obviousness of these claims by clear and convincing evidence.

760. Claims 1-3 of the '898 patent, which require obtaining a "predetermined molecular weight profile" through the use of HBr in acetic acid would similarly not have been obvious. Defendants have not established by clear and convincing evidence that a person of ordinary skill would have been motivated to set a predetermined molecular weight profile for copolymer-1 or that it would have been obvious that such a molecular weight profile could be controllably achieved through treatment of protected copolymer-1 with HBr in acetic acid.

761. None of the prior art references render obvious the use of HBr in acetic acid in order to control the average molecular weight or the molecular weight distribution of copolymer-1 or its intermediary, TFA-copolymer-1. Because Defendants have failed to prove that the process limitations requiring such a reaction would have been obvious, none of the claims of the patents-in-suit are invalid for obviousness on this basis.

(iv) Secondary Considerations Further Demonstrate Non-Obviousness

762. Secondary considerations further support the conclusion that the asserted claims are non-obvious. *See Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966); *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010). When present, secondary considerations "may often be the most probative and cogent evidence [of non-obviousness] in the record." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). Evidence of secondary considerations must be considered if present. *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1343 (Fed. Cir. 2010). These secondary considerations include commercial success of the claimed invention; the invention's satisfaction of a long-felt need in the art; the failure of others to solve the problem addressed by the invention; unexpected results and copying of the invention.

(1) Commercial Success

763. The commercial success of an embodiment of the claimed invention is strong evidence of its non-obviousness. *See Graham*, 383 U.S. at 17; *Arkie Lures, Inc. v. Gene Larew*

Tackle, Inc., 119 F.3d 953, 957 (Fed. Cir. 1997) (evidence of commercial success may be "highly probative of the issue of nonobviousness"). To establish commercial success, a patentee must show significant sales in the relevant market and a nexus to the claimed invention (that the success was due to the patented invention). *Rolls-Royce, PLC v. United Tech. Corp.*, 603 F.3d 1325, 1340 (Fed. Cir. 2010). "[I]f the marketed product embodies the claimed features, and is coextensive with them, then a nexus is presumed and the burden shifts to the party asserting obviousness to present evidence to rebut the presumed nexus." *Brown & Williamson Tobacco Corp. v. Phillip Morris, Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000). A successful product is "coextensive" with the claimed invention when it is commensurate in scope with the patented invention, as opposed to only a "component of a commercially successful" product. *Mitsubishi Chem. Corp. v. Barr Labs, Inc.*, 718 F. Supp. 2d 382, 437 (S.D.N.Y. 2010) (finding a pharmaceutical formulation "coextensive" with the asserted claims where it was an "inextricable and essential part of what doctors are prescribing" and "not a part that can be separated out from the remainder of the product"), *aff'd*, No. 2010-1432, 2011 WL 3288394 (Fed. Cir. Aug. 2 2011).

764. The significant sales and the growing market share of Copaxone® constitutes commercial success, and is further evidence of the non-obviousness of the asserted claims. *See Tec-Air, Inc. v. Denso Mfg. Michigan, Inc.*, 192 F.3d 1353, 1361 (Fed. Cir. 1999) ("Although sales figures coupled with market data provide stronger evidence of commercial success, sales figures alone are also evidence of commercial success."); *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 21 F. Supp. 2d 366, 374 (S.D.N.Y. 1998), *aff'd*, 231 F.3d 1339 (Fed. Cir. 2000) (finding that $1 billion in annual sales of Pepcid® despite pressure from competitors is clearly a sign of commercial success).

765. The unrebutted record evidence also establishes that Copaxone® meets the limitations of at least one claim of each of the patents-in-suit.[12] Clearly the claimed inventions are "an inextricable and essential part of what doctors are prescribing" when they prescribe Copaxone®. Copaxone® is, therefore, coextensive with the asserted claims. *See Mitsubishi Chem. Corp.*, 718 F. Supp. 2d at 437. Because Copaxone® embodies and is coextensive with the asserted claims, a nexus between commercial success and the patented invention is presumed. *See, e.g.*, *Rolls-Royce, PLC*, 603 F.3d at 1340; *Mitsubishi Chem. Corp.*, 718 F. Supp. 2d at 437-40.

766. When a patentee establishes a presumptive *prima facie* nexus based upon the success of a commercial embodiment of the claimed inventions, the burden shifts to the challenger to demonstrate that the commercial success results from a factor other than the invention. *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988). Defendants have made no such showing. *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 679 (Fed. Cir. 1988); *Brown & Williamson*, 229 F.3d at 1130 ("The presumed nexus cannot be rebutted with mere argument; evidence must be put forth."). Thus, a nexus exists between Copaxone®'s commercial success and the claimed inventions.

767. Even if some rebuttal evidence had been presented, the record reflects an adequate nexus between Copaxone® and the features of the claimed invention. Dr. Lisak explained that his prescriptions for Copaxone® have increased over time because of the clinical advantages of the product, and his testimony was consistent with the record evidence that the usage of Copaxone® has grown over time. (Sept. Tr. (Lisak) 119:8-120:9; Sept. Tr. (Congleton)

[12] The only apparent dispute on this point is whether the molar ratio of Copaxone® is "approximately 6:2:5:1." As set forth above, the Court has concluded that the accused products (continued…)

50:12-51:2.) This evidence demonstrates a nexus between the commercial success of Copaxone® and the properties of the patented inventions. *See Mitsubishi Chem. Corp.*, 718 F. Supp. 2d 382 at 438.

(2) Long-felt, Unmet Need

768. "Recognition of need, and difficulties encountered by those skilled in the art, are classical indicia of non-obviousness." *In re Dow Chem. Co.*, 837 F.2d 469, 472 (Fed. Cir. 1998). "The existence of an enduring, unmet need is strong evidence that the invention is novel, not obvious, and not anticipated. If people are clamoring for a solution, and the best minds do not find it for years, that is practical evidence—the kind that can't be bought from a hired expert, the kind that does not depend on fallible memories or doubtful inferences—of the state of knowledge." *In re Manhurkar*, 831 F. Supp. 1354, 1378 (N.D. Ill. 1993), *aff'd*, 71 F.3d 1573 (Fed. Cir. 1995). Where there is a long-standing need in the medical community for a safe and effective treatment for a particular disease, an invention that fulfills that need is often deemed non-obvious. *See Eli Lilly & Co. v. Zenith Goldline Pharmas., Inc.*, 471 F.3d 1369, 1380 (Fed. Cir. 2006) ("The record shows a long-felt need for a safer, less toxic, and more effective clozapine-like drug."); *Pfizer, Inc. v. Ranbaxy Labs Ltd.*, 405 F. Supp. 2d 495, 518 (D. Del. 2005) (finding that, despite other products available on the market, "Lipitor® satisfied a long-felt need in the medical community to provide patients with more effective statins to help them achieve their LDL goals"), *rev'd on other grounds*, 457 F.3d 1284 (Fed. Cir. 2006).

769. The facts show that by 1994, there remained a long, unmet need for an effective, safe and tolerable disease-modifying treatment for RRMS. (Sept. Tr. (Lisak) 125:25-127:14.)

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have a molar ratio of "approximately 6:2:5:1" and concludes that Copaxone® is also "copolymer-1" as that term has been construed.

The introduction of Copaxone® fulfilled long-felt unmet needs for: (a) an additional effective, safe and tolerable treatment for RRMS; (b) a treatment for RRMS with a unique mechanism of action that worked differently than interferons; and (c) a treatment that had a milder side effect profile than the interferons. (Sept. Tr. (Lisak) 125:25-128:25.) Copaxone®'s fulfillment of each of these long-felt needs are secondary considerations that further support a finding of non-obviousness concerning the asserted claims of the patents-in-suit. *See Eli Lilly & Co*, 471 F.3d at 1380 (Fed. Cir. 2006); *Pfizer, Inc.*, 405 F. Supp. 2d at 518.

(3) Failure of Others

770. The repeated failure of others to solve a problem addressed by an invention lends further support to the invention's nonobviousness. *See Graham*, 383 U.S. at 17 (the "failure of others" is a secondary consideration of non-obviousness). In the pharmaceutical industry, the failure of others to develop a safe and effective drug often supports the nonobviousness of a drug that finally achieves success. *See, e.g.*, *Yamanouchi Pharm. Co.*, 21 F. Supp. 2d at 374 (stating that the evidence showing that "the pharmaceutical industry at large was attempting to improve upon existing [anti-ulcer] drugs with only a small number of producers coming close to success" supports a finding of nonobviousness); *Eli Lilly & Co. v. Zenith Goldline Pharm.*, 364 F. Supp. 2d 820, 832 (S.D. Ind. 2005), *aff'd*, 471 F. 3d 1369 (Fed. Cir. 2006).

771. Evidence was presented at trial of drugs that showed initial promise for the treatment of MS, but that failed because of lack of efficacy or significant side effects. (Sept. Tr. (Lisak) 131:14-136:19; PTX 99; PTX 523; PTX 538; PTX 591; PTX 605; PTX 616; PTX 617; PTX 623; PTX 626; PTX 627; PTX 644.) There is undoubtedly an economic incentive to develop drugs to treat MS, yet the evidence of numerous failed therapies demonstrates the difficulty in developing effective therapies for MS. (Sept. Tr. (Lisak) 135:22-136:10; PTX 644 at 184.) Copaxone®'s success in light of these failed attempts provides further support for the

non-obviousness of the asserted claims. *See Yamanouchi Pharm. Co.*, 21 F. Supp. 2d at 374; *Eli Lilly & Co.*, 364 F. Supp. at 832.

(4) Unexpected Results

772. Unexpected superior properties or advantages of an invention are another secondary consideration of nonobviousness. *Procter & Gamble Co. v. Teva Pharma. USA, Inc.*, 566 F.3d 989, 993 (Fed. Cir. 2009). As the Federal Circuit has explained, "that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious." *In re Mayne*, 104 F.3d 1339, 1343 (Fed. Cir. 1997). Unexpected results may be shown with proof that (1) there is a difference between the results obtained and the closest prior art, and (2) the differences would not have been expected by one skilled in the art at the time of the invention. *Procter & Gamble Co.*, 566 F.3d at 997-98. The unexpected reduced toxicity of a drug as tested on animal models supports a finding of non-obviousness. *See, e.g.*, *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 536 F. Supp. 2d 476, 477-78, 496-97 (D. Del. 2008) (unexpected reduced toxicity demonstrated using a "short term toxicity screen" with rats), *aff'd*, 566 F.3d 989 (Fed. Cir. 2009); *Takeda Chem. Indus.*, 417 F. Supp. 2d at (unexpected lower toxicity demonstrated in mice and rat testing, as well as an *in vitro* chick lens assay).

773. The record establishes that low molecular weight copolymer-1 was unexpectedly superior to the prior art copolymer-1. The *in vivo* and *in vitro* toxicity data generated by the Weizmann scientists and Teva showed that the claimed lower molecular weight copolymer-1 had unexpectedly lower toxicity than higher molecular weight copolymer-1 batches. (*See, e.g.*, July Tr. (Arnon) 333:18-334:2; July Tr. (Pinchasi) 32:1-6, 33:6-35:5, 46:21-47:8, 48:4-49:11, 55:7-58:21, 59:1-70:11; PTX 54; PTX 53; PTX 40.) Dr. Baird considered these and other data, and explained that they established a trend of decreasing toxicity with decreasing molecular weight. (July Tr. (Baird) 603:20-605:18, 607:10-608:15; PTX 34T; PTX54; PTX 887 at 44.) Dr.

Pinchasi also described the existence of this trend and stated that the relationship between molecular weight and toxicity was "very unexpected" since nothing in the literature pointed the development team in that direction. (July Tr. (Pinchasi) 32:1-6.) Defendants' toxicology expert, Dr. Susan Rice, agreed that one of skill in the art would have no expectation with respect to how lowering the molecular weight of copolymer-1 would impact toxicity. (Sept. Tr. (Rice) 1046:25-1047:7.) The lower toxicity of the low molecular weight copolymer-1 thus is an unexpected result that provides further support for a finding of nonobviousness regarding the asserted claims. *See Procter & Gamble Co.* 536 F. Supp. 2d at 477-78; *Takeda Chem. Indus., Ltd.*, 417 F. Supp. 2d at 357-58, 385-86.

774. Teva's experience with TV-5010, a high molecular weight version of copolymer-1, provides further evidence of the unexpectedly superior toxicity profile of low molecular weight copolymer-1. The record shows that Teva dropped the TV-5010 project due to safety problems, including serious injection site reactions and deaths in animals, discovered during toxicology studies. (July Tr. (Pinchasi) 105:25-106:11, 110:11-111:9; PTX 158 at TEV002207062.) These results reinforce the trend observed by Teva of increasing molecular weight and increasing toxicity, and they provide further support for the unexpected results seen with low molecular weight copolymer-1. *Genetics Institute, LLC*, 2011 WL 3672474, at *14 ("[I]t would be error to prohibit a patent applicant or patentee from presenting relevant indicia of nonobviousness, whether or not this evidence was available or expressly contemplated at the filing of the patent application."); *In re Chu*, 66 F.3d 292, 298-99 (Fed. Cir. 1995) (noting that evidence supporting non-obviousness need not be contained within the specification).

(5) Copying

775. Additional evidence of the non-obviousness of the asserted claims is the deliberate copying of the inventions by both Defendants. *See Arkie Lures*, 119 F.3d at 957

(evidence of copying may be "highly probative of the issue of nonobviousness"); *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1328-29 (Fed. Cir. 2009); *Crocs*, *Inc.*, 598 F.3d at 1311 ("[c]opying may indeed be another form of flattering praise for inventive features"). "The fact that copying is likely to be present in many Hatch-Waxman Act cases does not allow the court to ignore the copying as evidence of nonobviousness" and in fact, in the field of new drug design, "the very need for copying results from and emphasizes the unpredictability of medicinal chemistry." *Eli Lilly & Co. v. Zenith Goldline Pharma.*, No. IP 99-38, 2001 WL 1397304, at *14 (S.D. Ind. Oct. 29, 2001); *see also Sanofi-Aventis Deutschland GmbH v. Glenmark Pharma., Inc.*, No. 07-cv-5855, 2011 WL 383861, at *9 (D. N.J. Feb. 3, 2011) ("Copying, as secondary considerations evincing non-obviousness, is [an] important part of demonstrating non-obviousness even in a pharmaceutical patent case against an ANDA filer because an ANDA filer is not *required* to copy.").

776. [redacted]

Mani Iyer, Momenta's Associate Director of Drug Substance Manufacturing and Development testified that Momenta followed Teva's patents on making low molecular weight copolymer-1. (PTX 960 (Iyer Dep.) at 5:18-6:11, 128:18-130:17.) The time and temperature Momenta originally used for its debenzylation step were copied directly from the '808 patent. (PTX 960 (Iyer. Dep.) at 146:25-148:11. [redacted]

[redacted] The import of such copying on non-obviousness merits even greater weight in view of Defendants' failed attempts to develop alternative processes. *Advanced Display Systems, Inc. v. Kent State Univ.*, 212 F.3d 1272, 1285-86 (Fed. Cir. 2000) (finding that "wholesale copying of the claimed invention" despite attempts to design around is evidence of non-obviousness). Further, it is clear that the defendants were aware of the '550 patent and its disclosure of higher molecular weight copolymer-1, but they chose to submit to the FDA applications to market a lower molecular weight copolymer-1 falling within the scope of the asserted claims. *Eli Lilly & Co.*, 2001 WL 1397304, at *14; *Janssen Pharmaceutica N.V. v. Mylan Pharma., Inc.*, 456 F. Supp. 2d 644, 671 (D. N.J. 2006) ("undisputed copying" by Mylan, among other ANDA filers, supported nonobviousness). This evidence of copying further supports a finding that the claims of the patents-in-suit are not obvious.

XI. CONCLUSION

777. The Court concludes that both Mylan's and Sandoz's ANDA infringe the asserted claims, and that none of the asserted claims are invalid or unenforceable.

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